Appendix A. Sample Questions for Key Informants

Key Informant Perspective	Sample Questions
Researchers and Clinicians (including Professional Societies and Organizations)	Guiding Questions 1, 2, and 4. In addition: 1. What outcomes should be prioritized? 2. In your experience, what MAT models of care have been particularly successful and why? 3. Are there models of care that are particularly suited (e.g., feasibility, applicability) for rural or other underserved settings? 4. How would you categorize the components of MAT models of care? 5. What MAT models of care components are most critical for effectiveness? 6. What are barriers to implementation of MAT in primary care settings? 7. What are specific barriers to implementation of community-based psychosocial programs in MAT? 8. How could barriers to implementation be overcome? 9. Are you aware of new or innovative models of care that warrant additional research? 10. What are key research needs to understand effectiveness and implementation of MAT models of care? 11. What types of study designs would be useful for studying new or innovative MAT models of care? 12. What is a meaningful length of follow-up? 13. Are there specific areas related to effectiveness or implementation of MAT models of care that have been sufficiently studied to warrant a systematic evidence review?
Health Policy and Implementation Arenas	1. What outcomes of MAT are important from a health policy/payer perspective? 2. What policies do payers put in place to influence use of MAT for treatment of opioid use disorder? 3. How are decisions to cover or implement MAT made at a policy level or at an institutional/clinical setting level? 4. What are some research questions about MAT that you would like answered to inform policy and implementation decisions? 5. Are you considering new policies to improve the use of MAT, particularly in primary care, including rural or other underserved populations? 6. What are cost and/or economic efficiency considerations that impact diffusion, decision-making, and/or conceptual thinking around MAT?
Patient Perspective	1. What values do patients place on various non-substance-use-related outcomes and how do patients weigh trade-offs related to different pharmacological and non-pharmacological approaches? 2. What factors or themes are most important to patients receiving MAT? 3. What components of MAT are important for patients to know, that they may not be aware of? 4. What common experiences do patients in MAT programs describe? 5. Should the use of MAT programs be expanded; and if so, what settings for patients are most amenable to the implementation of MAT? 6. What barriers do patients experience in obtaining MAT? 7. What suggestions do patients have for improving MAT models of care? 8. What are ethical, privacy, equity, or cost considerations that impact patient's use of MAT?

MAT = medication-assisted treatment

Appendix B. Search Strategies for Guiding Question 3

Database: Ovid MEDLINE

1 exp Opiate Substitution Treatment
2 exp Opioid-Related Disorders/dt, pc, px, rh, th
3 methadone.mp. or exp Methadone
4 buprenorphine.mp. or Buprenorphine
5 naltrexone.mp. or Naltrexone
6 suboxone.mp.
7 3 or 4 or 5 or 6
8 2 and 7
9 (medicat* adj3 assist* adj3 (treat* or therap* or regimen* or interven* or program*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab.
11 9 or 10
12 2 and 11
13 1 or 8 or 12
14 limit 13 to english language
15 exp Comprehensive Health Care/
16 exp Community Health Services/
17 exp Outpatients/
18 exp Ambulatory Care/
19 exp Ambulatory Care Facilities/
20 exp General Practice/
21 general practitioners/ or physicians, family/ or physicians, primary care/
22 exp Health Services Accessibility/
23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 (((primary or ambulatory) adj3 care) or ((family or general) adj3 (medicine or practice* or physician* or doctor* or practitioner* or provider*)) or outpatient* or ((communit* or comprehensiv*) adj3 (health* or care))).mp.
25 (rural* or underserv* or frontier* or (geograph* adj3 (isolat* or remot*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26 24 or 25
27 23 or 26
28 14 and 27
29 limit 28 to yr="2005 -Current"
30 limit 28 to yr="1902 - 2004"
31 limit 14 to systematic reviews
32 limit 14 to (controlled clinical trial or guideline or randomized controlled trial)
33 exp epidemiologic study/
34 14 and 33
35 Comparative Study/
36 14 and 35
37 exp "Outcome and Process Assessment (Health Care)"/
38 14 and 37
39 mo.fs.
40 exp Death/
41 exp Vital Statistics/
42 39 or 40 or 41
43 14 and 42
44 exp Evaluation Studies as Topic/
45 14 and 44

46 exp "costs and cost analysis"/
47 14 and 46
48 exp Sociological Factors/
49 14 and 48
50 exp quality of life/
51 14 and 50
52 exp health behavior/
53 14 and 52
54 exp attitude to health/
55 14 and 54
56 31 or 32 or 34 or 36 or 38 or 43 or 45 or 47 or 49 or 51 or 53 or 55
57 28 or 56

Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 [exp Opiate Substitution Treatment/]
2 [exp Opioid-Related Disorders/dt, pc, px, rh, th]
3 methadone.mp. or exp Methadone/
4 buprenorphine.mp. or Buprenorphine/
5 naltrexone.mp. or Naltrexone/
6 suboxone.mp.
7 3 or 4 or 5 or 6
8 2 and 7
9 (medicat* adj3 assist* adj3 (treat* or therap* or regimen* or interven* or program*)).mp.
10 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab.
11 9 or 10
12 1 or 8 or 11

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp Opiate Substitution Treatment/
2 exp Opioid-Related Disorders/dt, pc, px, rh, th
3 methadone.mp. or exp Methadone/
4 buprenorphine.mp. or Buprenorphine/
5 naltrexone.mp. or Naltrexone/
6 suboxone.mp.
7 3 or 4 or 5 or 6
8 2 and 7
9 (medicat* adj3 assist* adj3 (treat* or therap* or regimen* or interven* or program*)).mp.
10 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab.
11 9 or 10
12 1 or 8 or 11

Database: PsycINFO
1 exp opiates/
2 exp drug rehabilitation/
3 exp drug dependency/
4 2 or 3
5 exp drug therapy/
6 exp methadone maintenance/
7 methadone.mp. or exp Methadone/
8 buprenorphine.mp. or Buprenorphine/
9 naltrexone.mp. or Naltrexone/
10 suboxone.mp.
11 5 or 6 or 7 or 8 or 9 or 10
12 1 and 4 and 11

13 (medicat* adj3 assist* adj3 (treat* or therap* or regimen* or interven* or program*)).mp.
14 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab.
15 13 or 14
16 1 and 4 and 15
17 12 or 16
18 limit 17 to english language
19 exp Primary Health Care/
20 exp community services/
21 exp Outpatients/
22 exp outpatient treatment/
23 exp Maintenance Therapy/
24 exp Ambulatory Care/
25 exp Ambulatory Care Facilities/
26 exp General Practitioners/
27 exp Family Medicine/
28 exp Family Physicians/
29 exp Treatment Barriers/
30 exp health disparities/
31 exp health care utilization/
32 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 (((primary or ambulatory) adj3 care) or ((family or general) adj3 (medicine or practice* or physician* or doctor* or practitioner* or provider*)) or outpatient* or ((communit* or comprehensiv*) adj3 (health* or care))).mp.
34 (rural* or underserv* or frontier* or (geograph* adj3 (isolat* or remot*))).mp.
35 33 or 34
36 32 or 35
37 18 and 36
38 limit 18 to systematic reviews
39 exp treatment outcomes/ or exp treatment effectiveness evaluation/
40 18 and 39
41 exp "Death and Dying"/
42 exp mortality rate/
43 41 or 42
44 18 and 43
45 exp "costs and cost analysis"/
46 18 and 45
47 exp Sociocultural Factors/
48 exp socioeconomic status/
49 47 or 48
50 18 and 49
51 exp quality of life/
52 18 and 51
53 exp health behavior/
54 18 and 53
55 exp attitudes/
56 18 and 55
57 38 or 40 or 44 or 46 or 50 or 52 or 54 or 56
58 37 or 57

CINAHL
S1 (MH "Substance Use Disorders+")
S2 (MH "Narcotics+")
S3 S1 AND S2
S4 "methadone"
S5 "buprenorphine"

S6 "naltrexone"
S7 suboxone
S8 S4 OR S5 OR S6 OR S7
S9 S1 AND S8
S10 (medicat* n3 assist* n3 (treat* or therap* or regimen* or interven* or program*))
S11 ((opiate* or opioid* or narcotic*) n2 (substitut* or replac* or maint*) n2 (treatment* or therap* or regimen* or program* or interven*))
S12 S10 OR S11
S13 S1 AND S12
S14 S3 OR S9 OR S13
S15 S3 OR S9 OR S13
S16 (MH "Primary Health Care")
S17 (MH "Community Health Services+")
S18 (MH "Outpatients") OR (MH "Outpatient Service") OR (MH "Ambulatory Care Facilities+")
S19 (MH "Family Practice")
S20 (MH "Physicians, Family")
S21 (MH "Health Services Accessibility+")
S22 S16 OR S17 OR S18 OR S19 OR S20 OR S21
S23 (((primary or ambulatory) n3 care) or ((family or general) n3 (medicine or practice* or physician* or doctor* or practitioner* or provider*)) or outpatient* or ((communit* or comprehensiv*) n3 (health* or care)))
S24 (rural* or underserv* or frontier* or (geograph* n3 (isolat* or remot*)))
S25 S23 OR S24
S26 S22 OR S25
S27 S15 AND S26
S28 (MH "Systematic Review")
S29 (MH "Meta Analysis")
S30 (MH "Practice Guidelines") OR (MH "Guideline Adherence")
S31 (MH "Randomized Controlled Trials")
S32 (MH "Epidemiological Research+")
S33 (MH "Prospective Studies+")
S34 S28 OR S29 OR S30 OR S31 OR S32 OR S33
S35 S15 AND S34
S36 (MH "Outcomes (Health Care)+")
S37 (MH "Vital Statistics+")
S38 (MH "Evaluation Research+")
S39 (MH "Costs and Cost Analysis+")
S40 (MH "Socioeconomic Factors+")
S41 (MH "Cultural Values")
S42 (MH "Quality of Life+")
S43 (MH "Quality-Adjusted Life Years")
S44 (MH "Health Behavior+")
S45 (MH "Attitude+")
S46 S36 OR S37 OR S38 OR S42 OR S43
S47 S15 AND S46
S48 S15 AND S46
S49 S15 AND S34
S50 s48 NOT s49

SocINDEX
S1 (MH "Substance Use Disorders+")
S2 (MH "Narcotics+")
S3 S1 AND S2
S4 "methadone"
S5 "buprenorphine"
S6 "naltrexone"
S7 suboxone

S8 S4 OR S5 OR S6 OR S7
S9 S1 AND S8
S10 (medicat* n3 assist* n3 (treat* or therap* or regimen* or interven* or program*))
S11 ((opiate* or opioid* or narcotic*) n2 (substitut* or replac* or maint*) n2 (treatment* or therap* or regimen* or program* or interven*))
S12 S10 OR S11
S13 S9 OR S12

Appendix C. Summaries of Calls with Key Informants

Call #1

What MAT models of care have been successful, particularly in primary care, rural or underserved settings?

KI #1

- One particularly successful program integrated delivery of MAT with HIV, Hep C, and other testing and psychosocial services in the same building, along with residential or outpatient services.
- There is a devoted staff member that uses marketing materials designed to educate and combat the stigma associated with MAT that goes out into the community to inform/educate and recruit physicians to provide MAT services, either through their own offices or at a specialized treatment center.
- The integration/coordination, co-location in the same building, and dedicated staff are key to the success.
- There are also connections to the LGBT community.
- It also seems very important that the peer specialist/recovery coaches have MAT-lived experience, which helps reduce stigma and with engaging and retaining patients.
- Telehealth/telemedicine sessions are run by a peer recovery organization; there is a close connection between the physicians, recovery staff, and telehealth services.
- This particular setting is rural, but other similar programs have been urban. Urban settings have more of a challenge getting physicians on board, requiring a lot of information and education around MAT and the supporting research. Engaging with the 12-step community has been helpful.
- The physicians that prescribe medications for OUD are usually different than the physicians that provide STD testing. There is also a close relationship with physicians providing primary care services.
- Regarding settings, these are not specialty clinics necessarily, but are a mixture of outpatient clinics (methadone), office-based opioid treatment (OBOT) (buprenorphine), and some nonprofit organizations providing MAT (non- buprenorphine).
- MAT service delivery is provided in a variety of settings to include local health departments, private nonprofit entities, for-profit entities responsible for administering behavioral health services directly or through contractual agreements. These provider entities include substance use or mental health treatment provider agencies, health centers, Federally Qualified Health Centers (FQHC), and primary care. The models used by MAT-PDOA grantees include but are not limited to the following:
    a. Medicaid Health Home Model
    b. COR-12 approach and NIH's Comprehensive Drug Abuse Treatment model
    c. OBOT-8 Model
    d. Hub and Spoke Model
    e. Massachusetts Office-Based Opioid Treatment with Buprenorphine (MAT OBOT-B) Model

f. Non-EBP: Johns Hopkins School of Medicine Collaborative Opioid-Prescribing (CoOP) model of OTP-OBOT

- To assist with treatment engagement and retention, peer support specialists are critical. Warm hand-offs result in a greater likelihood of treatment engagement and retention.

KI #2

- Massachusetts has been providing OBAT (office-based agonist treatment) since 2003, a nurse-care model that teams up with a primary care physician, so a nurse can manage the treatment without overburdening physicians (like an HIV model of care). This way, we were able to recruit many providers including residents and although residents can't prescribe they work with the attendings, learn and then take it on after they graduate.
- We used community health centers willing to identify a nurse care manager dedicated to the model to treat 100 to 125 patients on buprenorphine along side waivered providers. We train the nurses in a day long training and then hands on shadowing and site visits .
- In this state, the nurse component is a billable piece in FQHC and CHCs, which makes this model sustainable. A medical assistant was then added for more cost-effectiveness, and we were able to treat a large volume of patients, allowing the nurses to now manage a caseload of 1:125 patients. The number of health centers has increased substantially since the start of the grant, health centers have added additional nurses beyond what the grant is reimbursing for as it is sustainable.
- There is paperwork to complete for the state that allows them to track treatment access and outcomes
- The epidemic hit the Northeast a lot earlier than other parts of the country. With the state supporting the start up in the health centers paying for the nurse and providing technical support it encouraged doctors to get waivered and treat patients in community sites.
- Are the community health centers using naltrexone? Yes, but more for alcohol than for opioids. All centers have to provide all methods of treatment. We do treat both but seems to have better follow up and adherence for those with alcohol use disorders than opioids The state data shows that patients in MA on Medicaid stay on vivitrol for an average of 2.4 months
- Who funds the nurse care manager? The initial model was 100,000 a year per nurse care manager and this covered 100% of most including fringe and benefits. Now the NCM is covered at 50% and the state is funding the medical assistants as the RN visits are reimbursable at the same rate as providers, so they can bill therefore sustainable and the MA is not billable
- Is the nurse care manager the primary contact for the patients? If the physician has a waiver, they would be the provider, but the nurse does all of the initial screening, intake, education, consents, sends for labs, urine according to a protocol, and the physician is involved as needed, sign off on all labs and notes, is connected electronically, by phone, and curb side in the clinic. The initial start up info is obtained by the RN and then the patient is booked to see the waivered provider for final clearance, approval for office based treatment, dx of DSM V for opioid dependence. Once approved the patient is booked to come back to see the nurse for the protocol driven induction where the patient takes their own meds, and then follows up with the nurse weekly until stable and then this progresses. Most health centers have at least two OBOT docs if not more.

- How are psychological services integrated? They are either on-site or nearby counseling services. Both we do a small amount on site and then have many services across the street specific to men and women
- If the patient receives buprenorphine, does that information appear in their health record? Yes, it used to be locked confidential notes, but that is now impossible due to Epic.

KI #3

- We have seen more models fail than succeed in Kentucky. There isn't a lot of state money given to support medication-assisted treatment . There is a lot of stigma attached to MAT and the doctors who prescribe it. However, there are some efforts to expand MAT within pregnant women through a federal grant that was recently awarded. It is yet to be seen how many women this will reach.
- Some models have been successful, but they may not be feasible to implement on a wide-scale because they are run in part by volunteers.
- For example, an obstetrician started a buprenorphine clinic within her OB clinic and found that you can treat opioid addiction in pregnancy effectively since the women have regular appointments at the OB clinic anyway. This clinic has an addiction expert and a neonatologist donating their time to the clinic. Group psychological therapy also occurs within the clinic but this is supported in part by a grant. Individual psychological treatment is referred out/ not integrated. This OB clinic is servicing many of the high risk opioid dependent women from the Eastern part of the state so women are sometimes traveling long distances.
- A young, family medicine physician is trying to open a buprenorphine clinic within her primary care clinic but is not expecting that reimbursement from payors will fully support the clinic.
- The OB bup clinic mentioned above is not billing any differently. Some Medicaid insurers are trying to get the obstetricians at this clinic to write mini-grants to support their services because the outcomes are good; but these physicians are already very busy. It is difficult to find bup providers to take over the bup prescribing/addiction treatment once women are postpartum. Medicaid has inadequate reimbursement and private clinics are going bankrupt that tried working with Medicaid. Some Medicaid MCOs put up barriers – e.g., prior-authorization form is 4 pages long. PA form questions are largely focused on preventing or reducing diversion. Several Medicaid payors are not responding to data on effectiveness of MAT. It is all about the immediate cost of providing addiction treatment which is new to KY – prior to the ACA – it was not a covered benefit.
- Is there a potential for midlevel providers to prescribe? This key information does not see the state being friendly to this idea.
- There was a recent grant to increase MAT in rural areas and there was not enough interest to support responding to it, although the state did receive a grant to expand MAT in pregnancy about a year ago.
- The research shows that the most robust risk factor for use of diverted buprenorphine was a failed attempt to access buprenorphine. People try to seek help for their addiction, but when they cannot access it, they will get the medication by other means which makes sense. We would do the same if we had diabetes and could not get into a doctor for insulin and proper treatment – we'd get insulin by any other means to try to do the best

we could (but of course it is not the same as getting medical treatment from a doctor knowing what dose, how to take, monitor etc).

KI #4

- A model in Vermont, the Hub and Spoke Model, has been getting traction. There is a centralized intake process, after which patients are connected to physicians in their communities to provide continued care along with primary care. This arrangement was set up within the state Medicaid plan.
- In addition, an individual went out and actively recruited doctors to get waivered during the early opioid epidemic, which led to many doctors with waivers. However, out of the doctors who get training, many never get waivered, and many prescribe very little or don't prescribe.
- Another model is the Medicaid Home Model for those with OUD, which has been underway in Rhode Island, Vermont, and Maryland. These are Medicaid Health Homes built around specialty treatment centers, where there is also a significant commitment to the primary care needs of the patients.
- Most states don't have any models like Massachusetts or Vermont.
- Vermont has also created physician treatment guidelines including primary care referral and the psychological component.

What barriers to implementation exist, besides lack of funding and reimbursement, lack of waivered physicians, stigma, being able to provide choices for patients, distance, anything else?

- The Wellstone Parity Act is grossly violated by insurance companies, and unless they are held accountable it will not change. There are onerous prior authorization requirements, and for minor reasons, prescriptions get denied and patients relapse. The insurance companies try to get away from paying with onerous requirements.
- Imposing additional (urine) mandatory quantitative testing also increases cost of care.
- The addiction crisis is out of control. Special teams are assembling in hospitals for injection issues for IV/opioid addicts with deep-seated infections (e.g., endocarditis, osteomyelitis) who have never been offered any evidence-based medical treatment.
- These patients can't get into skilled nursing facilities due to their addiction diagnoses.
- The 100 patient limit is a real economic disincentive for physicians and getting waivered.
- Patients don't want to be in the same waiting room as those with OUD, and therefore physicians have to set up multiple locations.
- The economics do not make sense, which is cited frequently by doctors.
- Rural cities seem to get inconsistent guidance from law enforcement agencies.
- Regarding telehealth/telemedicine, there is inconsistent guidance from the DEA.
- There is also a lack of contingency plan for the physician if the patients miss behavior therapy. There's no follow-up on referral. However, nurses and physicians can do very basic counseling. Medication management can be enough to get improved outcomes without the psychological component though. The data from studies evaluating treatment outcomes with enhanced counseling vs. med management alone have not shown differences between the two (Weiss, POATS study and Fiellin also had a published study).

- Need realistic diversion programs. Perfect treatment cannot become the enemy of good treatment.

Our task is to develop an organizing framework of the components in the models of care…

- KI's generally agreed with an organizing framework that includes the following components
    - Pharmacological component
    - Coordination/co-location/integration component; these are on a continuum with minimal coordination at the lowest end of the continuum and integration, which is often characterized by close collaboration, co-location, and shared systems (e.g., financial, EHR), on the high end or the goal/best.
    - Education component of clinicians with community buy-in and debunking of stigma.
        - Attitudes of the community are important; NIMBY still exists. Many communities don't want the treatment facilities in their neighborhood. Hence, a great deal of stakeholder education needs to occur with an emphasis on how delivering MAT services ultimately benefits the community.
        - Education of payers who run Medicare/Medicaid needs to be thought of more broadly.
    - Psychosocial component
        - Individual, group, family
        - Trauma-specific services are important for this population.
- Perfect treatment cannot become the enemy of good treatment

What are important outcomes to think about, from a policy perspective, and from a clinical perspective?

- Patients remaining in treatment. How do we measure retention?
    - Urine testing
    - Been in care for 12 months or more
    - Improved care of comorbidities
- Patients not dying
- The mortality rate is much lower for those who stay in treatment, and it has a strong correlation with a lot of outcomes: getting or keeping a job, not being arrested, basic life requirements like a stable family life.
- It is cost-effective, but the payers are ignoring this because in large part the behavioral health costs are in a different bucket of money than the medical costs (e.g., costs paying for the ER / hospitalization of an overdose, surgery for endocarditis) – the buckets are not talking to each other and the behavioral health bucket doesn't appear to get credit for saving costs in the medical bucket.
- We also need to look at nontraditional measures to determine quality of life; for example, is the person working, in school, or housed as a result, in part, of receiving treatment. We need to go beyond outputs (e.g., numbers of folks served or who remain in treatment) to outcomes (e.g., has the persons quality of life changed for the better).

- Need to review "Good Samaritan" policies and legislation in states.

What are the key research needs, what are the big gaps, where would funding be best invested?

- Cost-modeling to get payers/providers on board.
- Increase the supply of clinicians/prescribers available, especially in rural areas.
- Determining what can we do to improve/promote the use of MAT.
- Clarity on the relative importance and quality of all components.
    - Some insurance companies hold the psychological component as a requirement, as some states are concerned about the quality of care. People who get only the medication component also have good outcomes. More research on this may be helpful.
- Examining midlevel vs. physician based services on outcomes
- Strategies about how to work with patients who come in on benzodiazepines.
- For pregnant women, examining outcomes for the mother as well as the infant.
- Training the workforce
- Allow NP and PA's to prescribe
- Effectiveness of using peer recovery services as an additional outcome. To this KI knowledge there is a dearth of literature on this topic.
- There is a growing population of intravenous drug users in hospitals with deep-seated infections - can we show cost savings by treating these people? It's happening and there's not much on it.
- The best urine drug testing strategies are unknown, it would be good to know the outcomes, since urine testing has become a huge business. Maybe look at swabs the specificity seems to be getting better it would certainly make things a lot easier
- Bumping up care in SNF's allowing patients with SUD and on Bupe and Methadone to go to SNF's without current barriers
- The perfect is the enemy of the good. We may be able to define a perfect model, but it will miss reality and could create an excuse for not providing good care when the patient may benefit from good care. Some treatment is better than no treatment.

Should those abusing prescription medications vs. illicit drugs for chronic pain be researched separately?

- Yes, because the chronic pain sufferers have a more complicated treatment.
- PDMPs (Prescription Drug Monitoring Programs) can be a good tool for doctors if used in a therapeutic, not punitive way.

Next steps

- Notes from the call will be circulated; please let us know if anyone has edits/clarifications.
- The EPC may contact the KIs for additional questions.

- The KIs will also be invited to review and provide comments on the draft Technical Brief before it is finalized.

Summary of Key Informant Discussion #2

What Medication-Assisted Treatment (MAT) models of care have been successful, and what made them successful in your opinion, particularly in primary care, rural or underserved settings?

KI #1

- Our model is based in a rural setting with ~70% on methadone and ~30% on buprenorphine.
- Transportation is a major difficulty in this rural setting, where some people are traveling 1.5 to 2 hours one way and need to come in every day.
- The expertise and support for MAT in the larger the community is fairly light, even among some physicians. They would benefit from learning more about MAT in particular and addiction in general.
- A Hub and Spoke Center of Excellence model would work well in our case, since it would provide a lot of needed resources in one place. Patients would be evaluated, appropriate treatment could be determined, then they could be passed back to their primary care provider in 2 to 4 weeks if appropriate.
- A major barrier to provision of MAT in our setting is that physician assistants and nurse practitioners cannot prescribe buprenorphine.
- The limit of 100 patients per physician doesn't seem to be an issue here. A few might be approaching their limit.
- Barriers are that some primary care physicians don't want these people in their practice; we need models showing that these patients can be a rewarding addition to their practice.
- Stigma is huge here and goes beyond the physicians.
    a. There is a drug court judge who is firmly against MAT.
    b. MAT in a for-profit setting is a problem; it is hard to see a for-profit entity as a partner.
    c. Many providers of buprenorphine have a black and white viewpoint with rigid policies about when to taper down; and will cut patients off that don't meet those policies.
- We have a local organization of everyone that prescribes opioids that meets regularly. We see it as our responsibility to decrease mortality and morbidity related to prescription opioids. CMEs (continuing medical education credits) are offered. There is a huge amount of misinformation out there. Providers don't understand the latest thinking.
- How has the behavioral component been integrated?
    a. There is a disconnect due to stigma. Substance abuse treatment providers are often not very supportive of MAT, making collaborations between the substance abuse treatment providers and providers prescribing medications difficult.
    b. There is a licensed clinical social worker with experience in chronic pain treating patients for pain and addiction, not necessarily in MAT. There are a lot of different models being used to add psychology and counseling to MAT, especially in FQHCs (federally qualified health centers) and CCOs (coordinated care

organizations), and they have had varying degrees of success. The payment piece is an issue; what are we willing to pay for in terms of procedures?

- How have you dealt with the transportation issue? Have you used telehealth?
    a. Telehealth has not been attempted, but the CCOs will pay for transportation through Medicaid.
- Are you using Naltrexone therapy (injectable)?
    a. No, we have not figured out a way to pay for it.
- Both buprenorphine and methadone are provided at our OTPs (opioid treatment programs).

KI #2

- Our model is of MAT methadone and behavioral health integration in primary care, so mostly buprenorphine.
- Cambridge Health Alliance consists of 3 hospitals and 12 primary care sites.
- At primary care sites, "care partners" are usually Master's level individuals that assist the primary care staff with screening, brief intervention, and referral to treatment.
- The model also includes integrated behavioral health specialists who have Master's or PhD's degrees working in primary care sites to do brief psych treatment.
- Primary care physicians generally prescribe Suboxone or Vivitrol.
- A training program exists to get more physicians, especially residents, and also faculty on board.
- The model that seems to work the best is co-led by a behavior health specialist and a primary care provider. It includes monitoring, brief intervention, the identification of people who could be treated in primary care, making sure they have followed up with and that they receive behavioral health interventions. It also identifies people who need a higher level of care, who are expedited into an OTP (Opioid Treatment Program).
- However, the OTP/specialty treatment center cannot prescribe Suboxone, Vivitrol, or buprenorphine; therefore, patients must switch to methadone. Patients don't have the capacity to go back and forth between primary care and the specialty setting, because they must switch medications. It's a huge barrier. Most of the OTP patients cannot be stabilized in the primary care setting for various reasons; too many comorbidities.
    - To clarify, at a community health center or FQHC, or hospital, buprenorphine can be prescribed because you have access to codes that you don't have access to in the OTPs.
- A model like the co-op in Baltimore or the hub and spoke in Vermont is what we would like to do, so that people could go back and forth between settings as needed.
- The issue is reimbursement.
    - A challenge in primary care settings is that while OBOT (office-based opioid treatment) nurses can provide support services to physicians, they don't have a rate within the state of Massachusetts.
    - OTPs don't have a rate to be able to pay for it.
    - This is something they are working on and trying to figure out.
- The Suboxone physicians need someone who can do urine screens, follow-up, and help link patients into other community resources like assistance with housing (a case manager), but don't need a Master's or PhD level psychologist. Other patients need both a case manager and a therapist; these are two different roles.

- Transportation is also an issue, even in the city. Especially in the out-patient programs. Providing psych services at the primary care site increases the chances of getting care.

KI #3

- More collaborative models of care are needed.
- Agree that there is stigma. Many primary care physicians do not have the expertise needed to treat these patients. A similar model to what has been used for depression might be useful.

What barriers to implementation exist, besides lack of funding and reimbursement, lack of waivered physicians, stigma, being able to provide choices for patients, distance, anything else?

- Patients who are co-prescribed or taking elicit benzodiazepines and opioids need a lot of services to get off of benzodiazepines and use MAT.
- In Massachusetts, detox programs do work with OTPs with methadone while they taper off benzodiazepines. However, the length of stay is not adequate enough to get off of benzodiazepines. Insurance doesn't want to pay for it.
- Benzodiazepines are a huge barrier to OTP MAT treatment.
- There is a philosophical disconnect between OTP and residential programs, and Massachusetts has worked to break down some barriers, but some still exist. Alcohol is an added issue.
- In some instances the DEA (Drug Enforcement Agency) has visited physicians and this has made some reluctant to prescribe.

Is the 100 patient limit a barrier?

- We don't have the limitation for those working in OTP, and in primary care people are not working at their capacities, where they don't have the amount of support services to get them to their capacity, and also physicians don't want to treat that many.
- On the other hand, some physician groups are doing a lot of prescribing and not a lot of treatment/follow-up. The Clean Slate Addiction Treatment and Rehabilitation Centers in Massachusetts are a for-profit community of physicians who do a lot of prescribing and not a lot of treatment. They put a lot of buprenorphine in the hands of patients who need more structure. Patients from OTP say they can't handle the prescriptions.

What are the key research needs, what are the big gaps, where would funding be best invested?

- Multiple KIs agree that more research is needed for patients who have cormorbid addiction and chronic pain.
    - More research is need on the prescription and management of chronic pain; there is pain with addition and just addiction, which are different populations.
    - Multiple KIs agree there are too many people on high doses of opioids for chronic pain.

    - We have had a lot of success using buprenorphine to taper opioid doses. Need more research on how it is done, on morbidity/mortality outcomes, and how to get it paid for.
- We don't have good data on the things that influence policy makers. How many primary care providers are at their 100 patient limits? How many patients are there in treatment; is there a registry? There are big data gaps.
    - Buprenorphine is included in the PDMP (prescription drug monitoring program), unless it comes from OTP, and methadone is not included in the PDMP unless it's prescribed for pain. This is something that comes up in the ER, and if data is not shared, primary care doctors may not know that a patient is in an OTP.
- Multiple KIs agree that more research is needed on effective models and management strategies in patients with comorbidities.
- It would also be helpful to have more research on the length of retention in treatment, how to keep people in treatment and prevention of overdoses.
- From the other KI call, cost-modeling, understanding the effectiveness of midlevel prescribing, the benzodiazepine issues, and the management of pregnant women were mentioned as areas for future research. Agree.
- Accessibility to psychiatrists to manage psychiatric comorbidity is also needed.
    - Is teleheath worth researching for psych services?
        - This is a very exciting area, yes. Cambridge has been doing some psychiatric consultation via ipads.
- Additional comment emailed after the call: We might think about how we decide who should be admitted to which medication-assisted treatment. For example, are there criteria (other than anecdotal) for who's best suited for buprenorphine vs. methadone treatment?

Our task is to develop an organizing framework of the components of the MAT the models of care, and previous KIs thought were there were the following components:

- **drug (Vivitrol, buprenorphine, methadone)**
- **integration**
- **psych**
- **education/outreach to decrease stigma/increase uptake and the increase the number of waivered physicians**

And, they also thought that some components are better than nothing. Do you agree?

- Is giving the medication only better than no treatment, as previous KIs mentioned?
    - KQ #2: I have a strong opinion against prescribing alone. Medication without the behavioral component is not treatment. However, not everyone needs the same level of care. I worry about a message that says that medication alone is okay. Some patients will not take the medication and instead sell it, they need more help. A study of the Medicaid population in Pennsylvania by Gordon et al emphasized that people don't do well without the behavioral health component. The data was from 2007-2012. Title is Patterns and Quality of Buprenorphine Opioid Agonist Treatment in a Large Medicaid Program, published in the Journal of Addiction Medicine.

    - KQ #3: Ideally you would have both, the medication and psych components, but I would want to make sure that people get the treatment that they need, even if it is just medication.
- 42 CFR (federal opioid treatment standards) creates a silo to integrating services and communication; so everyone can't know what others are doing.
    - There is a challenge in communication/collaboration that is key. Some programs require that patients give permission to be in communication with their primary care physicians.
    - There is a worry about stigma and others having access to their information. If primary care physicians know that patients are on MAT, they worry that they may not get sufficient pain coverage.
- There is another piece where providers themselves are placed in situations where they are uncomfortable; prescribers are learning and growing at the same time. Providers need education.
- Societal viewpoints need to change as well.

What are the important outcomes (other KIs previously discussed retention, mortality, quality of life, including work and relationships)?

- Retention.
- The use of ineffective interventions, which can be measured by repeated ER visits, acure care hospitalizations.
- Other drug use, overdose, HIV rates, quality of life, employment, criminal activity.

What are key policy areas to increase implementation and uptake?

- In some states, commercial payers are reimbursing for buprenorphine and Vivitrol, but methadone treatment is a struggle, this is a big issue. Multiple KIs agree that all levels of MAT should be available through Medicaid, Medicare and through commercial coverage.
- Multiple KI agree that physician assistants and nurse practitioners need to be buprenorphine providers. In some states they can prescribe, but only specific medications.
- The treatments should not require prior authorization.
- PDMP monitoring should be required.
- Insurance shouldn't have authority over automatic time limits for medications or limits on dose. This puts prescribing into the insurance companies hands. They want tapering.
- Want what OPCs offer in primary care, but confidentiality should be ensured in some way due to stigmatization.
- Reimbursement is crucial.
- Quality of care needs of services and retention needs to be measured, or people will not provide good treatment.
- In some states/counties, CCOs (coordinated care organizations) are paying for buprenorphine treatment with no prior authorization waiting time, but we haven't pursued this for Vivitrol.

- In some states, police are coupling with providers to provide access to Vivitrol in lieu of going to jail.

Next steps

- Notes from the call will be circulated; please let us know if anyone has edits/clarifications.
- The KIs will also be invited to review and provide comments on the draft Technical Brief before it is finalized.
- If anyone has additional thoughts, please send us an email
- Thank you.

Summary of Key Informant Discussion #3

What Medication-Assisted Treatment (MAT) models of care have been successful, and what made them successful in your opinion, particularly in primary care, rural or underserved settings?

KI #1

- For many practices, this includes a physician working with a non-physician, which makes it easier for the physician to feel comfortable incorporating MAT into their practice.
- The nurse (or other non-physician staff) can assist the physician with the induction (nurse, PA, NP), patient follow-up, urine screens, psycho-educational counseling, and phone calls between visits. The physician can leave a printed prescription for them to provide to the patient, this person can collect the urine, and this allows the patient to get a refill without the need for a physician visit. This model was used in the BHIVES HRSA demonstration project, which had10 sites.
- Did the nurse do the initial screening?
    a. They could, over time, develop some skills in initial assessment, but there is always an initial visit with a physician to confirm the diagnosis, take a detailed medical and psychiatric history, and make a determination regarding prescribing. It could be a nurse, nurse practitioner, physician's assistant, social worker, etc. that could develop some of these skills needed by the non-physician "glue" person.
- Did you have any trouble recruiting physicians for this project?
    a. The sites all applied for a grant through HRSA, and had varying levels of experience; most had not prescribed Buprenorphine previously.
- Are you using Vivitrol?
    a. No, not for opioid dependence. I haven't found the patient population that could do 5-7 days abstinence following tapered doses to allow them to be eligible for naltrexone injections.
- Other Key Informants have mentioned stigma or resistance as a barrier, has that been your experience? Some have also mentioned that education/outreach as important in making a model work…

    - It depends on where you are. There is a spectrum of comfort, some physicians are committed to treatment; some are comfortable with it for short periods of time.
    - In Scott County, Indiana after the recent outbreak, after an 8 hour buprenorphine training with 5 or 6 local physicians in the audience, none were interested in prescribing buprenorphine. There are very large cultural, philosophical, and almost religious barriers to the use of opioid agonists for the treatment of opioid use disorder. Some were interested in naltrexone and talked about ways that they could integrate that into the criminal justice system.
- The "glue person" does management, follow-up, and some counseling, but are there also psychological services integrated the clinics for people who need more?
    - This can be a challenge, even more so in rural settings.
    - It varies based on level of resources. The physician and nurse can assist with psycho-educational services if they're trained, including motivational enhancement therapy, cognitive behavioral therapy, and patient education. Others on site may also assist, but are typically not very experienced in opioid agonist treatment. More experienced counselors are available at opioid treatment programs, but that's where lack of insurance or patients not being interested can be barriers.
- Can you comment on the study concerning higher and lower intensity counseling around buprenorphine?
    - Yes, there is a fairly extensive literature looking at varying levels of counseling and services provided along with opioid agonist treatment. A Cochrane systematic review failed to demonstrate beneficial treatment outcomes in a dose response manner with an increase in psychological services beyond medical management from their provider.
    - Another publication from a few years ago failed to find benefit over provision of medication alone.
    - Another study from 2006 of patients without untreated comorbid psychiatric or substance use disorders failed to find a benefit on retention or illicit opioid use when patients were randomized into groups who received 1x/week counseling from nursing staff versus 3x/week counseling (both with medication) over 12 weeks.
    - Another study of cognitive behavioral therapy administered by masters and doctorate level counselors failed to demonstrate a benefit on retention or illicit opioid use over medical management as well.
    - It seems that provision of medications, with a basic level of clinical management (care from a provider) is adequate for many patients.

<u>KI #2</u>

- My experience has been with the Ryan White funded clinics through HRSA's Special Projects of National Significance. These are models that include the glue person, who may be a medical case manager and sometimes a peer manager, who decrease the burden on a clinic and keep people in care better.
- In Indiana after the outbreak, a mental health agency, LifeSpring, developed a multiservice site called the One-Stop Shop. It is a unique situation because it was a mental health agency that applied for an expanded access grant to add primary care

services; it is co-located with a syringe exchange program. LifeSpring is providing mental health services (an addiction psychiatrist came in from Indiana University once a week), MAT, and HIV/Hep C treatment (infectious disease physicians were also coming in from the university once a week, but this has changed and may change again). They added social workers and a peer navigator to relieve the burden of the physician in charge. In this situation, the HIV and Hep C outbreak was due to injection drug use. The setting of the mental health center helped destigmatize getting these people into MAT treatment. The county also has a mobile van that is part of the syringe exchange program, that goes out into the community; this has also helped decrease stigma and get people into care.

- KI #1- This was a unique situation isolated to one town where all hands were on deck. I question whether we can develop policy and extrapolate based on this model.
    - KQ #2: This is true, but it is an interesting situation to look at, and does illustrate the challenges and logistical issues that physicians face in incorporating MAT in rural health centers, such as shared waiting rooms, additional staff needed, stigma, space, and integrating a population that is not easy to keep in care. Some primary care physicians set up MAT themselves, from the grassroots up, because they see the problem and feel that they need to do something; there is a lot of resistance though.
- In a program model developed in Western Virginia, a family physician named Art Van Zee saw a spike of overdose deaths and opioid addiction, and set up a practice with buprenorphine in his family practice.

How do you manage patients who need a continuum of care?

- Some patients can do well in a low resource setting like primary care setting. In my experience, 1/3 of patients will stop using, 1/3 of patients will decrease their use of opioids substantially, and 1/3 of patients will not do well.
- Life Spring also did inpatient care, although there was a 6 month waiting list. Expanding the level of care was difficult.
- What do you do for patients that can't be handled by a primary care physician?
    - The Physicians Clinical Support System for Buprenorphine (PCSS-B) was based on early experience training physicians. We noted that they needed additional support following the 8 hour training so we developed it as a mentor network. New Mexico's "ECHO Model" project also helps physicians get started. The provision of support services was built into the training - a mentor network for the physicians was part of the model and it required mentored practice, so physicians don't feel that they are on their own.

What are some of the ways that PCSS MAT and PCSS Opioids have been successful?

- It has changed over time. There used to be just the 8 hour training, but now there is an infrastructure of doctors who provide support after the training is over. One challenge is making sure that the mentors are doing a good job. PCSS does a good job at the national level for education, but it needs to get back to a more local level. We could use a cost-effectiveness analysis to determine its value.

What barriers to implementation exist, besides lack of funding, reimbursement, space, lack of waivered physicians, stigma, being able to provide choices for patients, distance, anything else?

- We are providing remedial education to physicians due to the current educational system. The current physicians did not learn about addiction in medical school or residency, that it's different from physical dependence, about treatment planning, the role of medications. This information can reduce stigma.
- There is also a huge amount of misinformation among family and patients.
- Diversion is a huge issue. As we move forward with increasing the number of prescriptions, we could circle back and create more harms though diversion.
- Other KIs have also mentioned reimbursement as a barrier, including dosage limits, treatment duration, and issues around prior authorizations.
    - Agree, reimbursement, especially with models with a glue person or peer navigator is a barrier.
- Other KIs have also mentioned the difficulties around the waiver process and limits to number of patients that can be treated.
    - If there was a tiered system that allowed providers to see a greater number of patients based on demonstrated competence, competency-based prescribing, that would be helpful.
    - Another issue is the physicians who get a waiver, but never implement it due to fears of DEA investigation for diversion.
    - Does HRSA have a position on the Treat Act?
        - I cannot comment on HRSA's position. I feel that it is important to look at all appropriate ways to expand treatment.
    - At any time the secretary could do away with DATA 2000. I worry about quality over quantity. There are plenty of reports about lucrative physician practices. Some groups hire additional doctors who can prescribe in order to make more money. We need demonstrated consider competency-based prescribing and greater self monitoring by the medical profession.

What are the key research needs, what are the big gaps, where would funding be best invested? Other KIs have mentioned that research is needed on: nurse practitioner/physician assistant prescribing; additional complexities for managing treatment for those with both addiction and chronic pain, those on benzodiazepines, those with alcohol addiction; PDMPs; sharing of patient information about MAT between PCP and OTP; cost effectiveness; MAT and pregnant women; and telehealth/telemedicine. Do you agree? What are other areas with research gaps?

- Youth are a challenging patient population, especially coming up with an appropriate management plan when parents are involved and patients may not be appropriate for long-term opioid agonist treatment.
- Other KIs have also mentioned that methadone is used in primary care internationally, and that there needs to be more research around whether a patient may benefit from trying a different pharmacological agent. Currently in the US, if patients switch pharmacological agents, they have to switch settings too.

- There also needs to be more research around the initiation of bupe in the ER with follow-up in primary care.
- All of the gaps that need to be considered have been touched on.
- Cost reimbursement and cost analysis will be key to getting insurance companies on board.
- This field needs to move to basic implementation science frameworks, as opposed to efficacy or effectiveness studies.

Our task is to develop an organizing framework of the components of the MAT the models of care. Previous KIs have mentioned the following components: 1. medication, 2. "glue person" (coordination/integration), 3. psych services, 4. education/outreach (to physicians, patients, the community), and possibly a 5th component, which is access to higher level care for those who cannot be safely treated in primary care

- This sounds comprehensive.
- A lot of what we discussed fall into these categories.

What are the important outcomes for clinicians or policymakers? (Other KIs have previously discussed retention as the main important clinical outcome and a proxy for other important outcomes; also, utilization measure, drug use, overdose rates, cost.)

- The Addiction Severity Index with its 7 domains: Drug use, psychosocial function, criminal involvement, employment, comorbidities, family and social relationships, etc.
- Retention is an important outcome and a big challenge.
- Nothing to add, retention is key and all other outcomes follow (e.g., homelessness rates).

What are key policy areas to increase implementation and uptake?

- Incentivize that federally qualified health centers or programs that receive Ryan White funding have 1 or 2 prescribers who actually prescribe.
- Cost remains a big barrier. Some patients don't have insurance and pay out of pocket and generics aren't necessarily cheaper.
- Monitoring diversion will be a huge policy issue. Someone who needs the medication often access it through someone sharing or selling it.
- Agree that diversion is big. I have mixed feelings about the Ryan White idea because implementation is difficult. Strategic implementation in certain populations might be an easier sell – in demonstrated areas of need.
- Is it too early to have physician assistants and nurse practitioners prescribing buprenorphine? They are able to prescribe other medications, including schedule II opioids, in some places, but what are your thoughts in terms of policy changes?
    - It depends on the person.
    - States vary widely in what is allowed. More research in that area will make it an easier sell.
- The extent to which we have poor prescribing practices within the medical profession. We are constantly hearing about physicians doing a bad job. In

Canada practices are monitored by colleagues and there are systems in place to identify and resolve bad prescribing behavior.
    - It sounds like the questions we need answered are: How do you measure quality? and What do you do about it?
- Both KI are in favor of limiting or curtailing arbitrary limitations in doses and time limits which create barriers to effective treatment.

The systematic reviews we have are all focused on the drug piece and it sounds like on the intensity of psychological services. What other areas are ripe for a systematic review?

- The Project ECHO support networks/models that are used for HIV and Hep C would be good to research for addiction.
- The issues around diversion are an important theme.
    - This is an area where either extended release MAT or thrice weekly observed dispensing or pharmacy-based dispensing (like the European models) of buprenorphine could be beneficial.

Does HRSA have any data on the prevalence of MAT dispensing from the Ryan White programs?

- They report an "encounter," which can be anything from meetings with counselors, support groups, or meeting with a physician for MAT. This would be a good research question.
- Some surveys have been done using FQHCs by Michael Lardiere at NACHC and also John Muench from OHSU.
- The following link was shared after the call: https://www.nachc.com/client/NACHC%202010%20Assessment%20of%20Behavioral%20Health%20Services%20in%20FQHCs_1_14_11_FINAL.pdf

Next Steps

- Notes from the call will be circulated; please let us know if anyone has edits/clarifications.
- The KIs will also be invited to review and provide comments on the draft Technical Brief before it is finalized.
- If anyone has additional thoughts, please email.
- Thank you.

Summary of Key Informant Discussion #4

What Medication-Assisted Treatment (MAT) models of care have been successful, and what made them successful in your opinion, particularly in primary care, rural or underserved settings?

KI #1

- I have seen a variety of different models. Opioid treatment programs (OTPs) with comprehensive care are the most effective; this not just a prescription for medication but includes ongoing counseling, social support, group therapy, drug testing requirements, nurses trained in addition medicine, etc. The OTP I run has methadone and buprenorphine, and we're looking at adding Vivitrol.
- Office-based buprenorphine models can be just as effective when done the right way, but the concern is that under DATA 2000, the requirements for OTPs are only recommendations for office-based providers. This creates a lot of room for not great quality care. There is one example in rural Tennessee where a physician with a DATA 2000 waiver meets patients in a church parking lot every month and writes prescriptions out of his car. He gives everyone the same dose. There is no drug testing, no referral to counseling or psychosocial support, no follow-up, and no other intervention. This is legal under the current system. However, these patients have no shot at recovery.
- I am an advocate for expanding access. However, if they raise or lift the 100 patient limit, they need to change the recommendations to requirements for primary care prescribing. Big pharma has a vested interest in lifting that cap. Lobbyists influence Congress. I'm fearful that this situation will create negative outcomes that will further stigmatize MAT.
- MAT is effective when you do what evidence suggests works- prescribe an adequate dose, treatment planning, psychosocial support, peer-to-peer support, etc. When you have all of those components together, you see recovery. The problem is that MAT could mean many different things because there is so much room for variation. It doesn't need to be as overly regulated as OTP, but I don't think we are doing a service to just prescribe. There needs to be quality control and inclusion of the coordination, psychosocial, and peer-to-peer components.
    a. Cognitive behavior therapy (CBT) is very important, but "counseling" is sometimes just case management- to help patients find resources.
- Methadone can be prescribed in primary care in the United States, but it's only done in New York City and Baltimore (pilot studies).
- Some of the large office based buprenorphine providers that are waivered will contact the joint commission or other accrediting body about what they need to do to become accredited. They find out about the costs and the other standards, and a lot don't end up doing it because it's optional.
- Question: Are there key components of MAT that patients aren't aware of that would be helpful?
    - This illness and treatment is a metabolic disorder. In treatment for most other disorders, like diabetes, there is a bigger emphasis on patient education and involvement, but MAT patients in many cases don't understand their condition or the medication. Many think it's a substitute drug, not a legitimate medication. There are a lot of providers that do great patient education and family education, but unfortunately MAT providers sometimes don't grasp the science. We should provide treatment and compassion.

KI #2

- I am currently writing a review with Roger Weiss on what the role of counseling should or should not be in MAT. We need to make it clear that we need some good data and

some clear outcomes. It is difficult to get any sense of a common outcome and the studies are not great (is it really intention-to-treat?). It is not possible to create a simple table of positive urine tests and 6-month outcomes.

- The role of counseling is complicated. Four studies by Lien, Fiellin and Weiss say that adding counseling to medical monitoring doesn't add a whole lot. However, the counseling is on top of twice weekly urine screens and once weekly physician meetings. An equal number of studies say that behavioral therapies do help, although there is some drug company involvement... Some patients do respond well to good medical monitoring, but for others this is not adequate. Counseling also varies from good to terrible. We need literature on who responds well to medical modeling. The role of self help is also important.
- Question: Where you practice, is there a main coordinator or glue person, and how are psychological services integrated?
    - Referring out just doesn't work, counselors need to be on-site, but it's not always feasible or cost-effective for your average office-based physician. I've come up with computerized CBT to reach people in rural settings or people who don't want to come in. That seems to work really well.
    - A "step-care" model that we use also works well, with an increase in intensity or frequency for those who need it. For those with clean urines, they need less intensity.
    - We need to figure out what a good outcome is- it has to be more than just retention.

What would you list as key outcomes?

- Need more than just retention; such as whether patients are: in treatment, not using opioids or other drugs, have a job, have a place to stay, getting medical care, and are out of jail.
- Agree- I would use the Addiction Severity Index. We look at all of these outcomes at intake and track them. If we see improvement, we are headed in the right direction.
    - Also, overall quality of life; even if urines aren't completely clean, patients can still be moving in the right direction.
- There is no cookie cutter approach, patients differ. We can't completely compare OTPs and primary care settings because the patients are different.

What are the major barriers to implementation of MAT in office based settings?

- Several surveys on this exist from physician groups. Some barriers include lack of access to good social services, concerns of stigma (don't want "those people" in their offices), don't have coordinating people, worry of things going wrong.
- Some physicians with waivers don't prescribe much.
- Question: Are there reimbursement issues?
    - Connecticut is pretty far ahead of the curve, so reimbursement is not really an issue here.
    - In Georgia and Tennessee, the vast majority of patients are self-pay, and buprenorphine is expensive. Medicaid has not been expanded.

- There is a great review by Johnson in the Am J Prev Med with data by state.

What are the key research needs, what are the big gaps? Other KIs have mentioned:

- **Need to ensure quality of care, and figure out how to measure it**
- **Additional complexities around managing addiction with chronic pain, benzodiazepine use, and/or alcohol addiction**
- **Mid-level prescribing, such as by nurse practitioner and physician assistants**
- **Understanding to what extent psychosocial services are needed, and for whom?**
- **Cost modeling/cost effectiveness**
- **Telehealth**

Do you agree? Is anything missing?

- This is a great list. I didn't hear how long should treatment should go on? At best, there is a 50% retention rate at 6 months. What should we be aiming for? My rule of thumb how long you're addicted is how long you should be treated as a rough estimate. The taper and drop off points are the most dangerous times. There is significant morbidity and mortality.
- Agree with the above. Also, where is the data behind DATA 2000? Buprenorphine in the office-based setting doesn't have much data at all. We need to figure out why that is. What is the resistance?

Our task is to develop an organizing framework of the components of the MAT models of care, and previous KIs suggestions the following 4 or possibly 5 components:

1. **Medication**
2. **Integration/care coordination (taking care of the person as a whole)**
3. **Psych services (broad spectrum)**
4. **Education/outreach to both patients and providers, to decrease stigma, increase uptake, and the increase the number of waivered physicians**
5. **Possibly, also that some patients are too complicated to be managed in an office-based setting; some referral to OTP for more intensive/sophisticated treatment?**

Any comments? Is there anything else we should be thinking of?

- This sounds pretty good.
- Regarding education, there are some really good studies from Australia and England showing that patients don't have a clue about treatment.
- There is an interesting literature on starting patients on treatment in the emergency department. There is a really high drop-out with that strategy. Strengthening those linkages is important.
- I would add the adolescent/emerging adult population. Figuring out how to provide buprenorphine to these patients is problematic, and the problem is huge.
- I'd frame #5 similarly to the management of a chronic disease that gets better or worse sometimes. This is very consistent with treating addiction.
- Question: Regarding #5, are there any existing criteria for stratifying patients to appropriate care?
    - No, this is clearly a gap. We came up with a little checklist with questions like: Do they have support? A place to live? Are they ready to taper off? Do they need more care?

What are key policy areas for improving access to MAT? Previous KIs have mentioned:

- **No automatic time limits**
- **Not requiring onerous prior authorizations**
- **States vary in who can prescribe**
- **Increasing the pool of providers**
- **Reimbursement**

- Need to be able to get people into care. It various by state. Getting people into care, affordability and insurance are barriers.
- The issue is primarily quality. See Dr. Mark Willenbring's profile in the New York Times today (http://www.nytimes.com/2016/02/23/science/mark-willenbring-addiction-substance-abuse-treatment.html?_r=0) He is using evidence-based therapies with success and says the for-profit 28-day programs do not work. We need to move the waste into something that really works. And maybe put restrictions around the things that do not work.

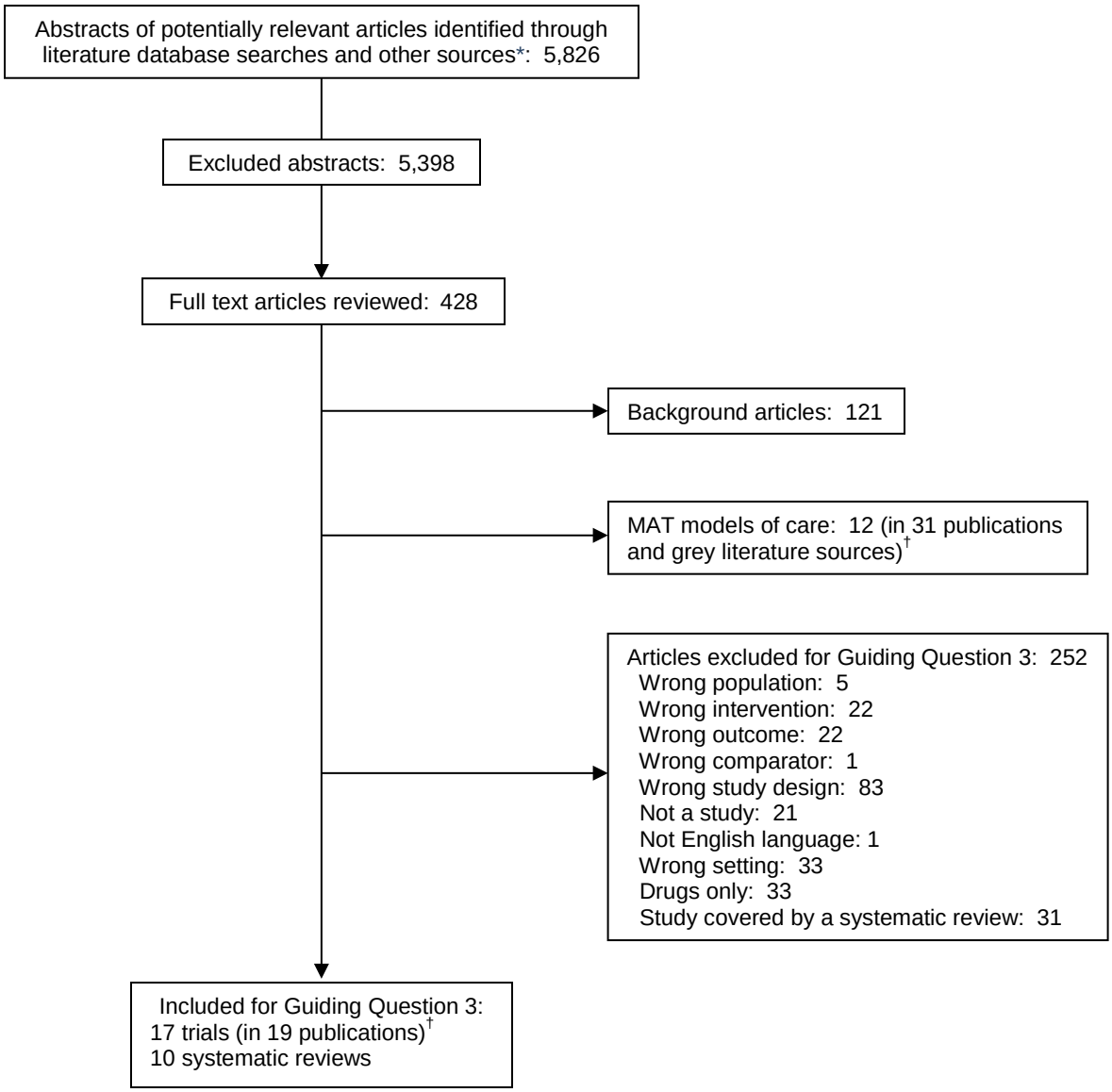
Naltrexone is underutilized, why?

- Naltrexone can be appropriate and effective for a small, specialized population.
- Mostly, patients do not want to take it.
- It may also not be pharmacologically correct.
- Pharma money influences things.
- The criminal justice system's version of MAT is forced Vivitrol, and that needs data.

Next Steps

- Notes from the call will be circulated; please let us know if anyone has edits/clarifications.
- The KIs will also be invited to review and provide comments on the draft Technical Brief before it is finalized.
- If anyone has additional thoughts, please send us an email
- Thank you.

Appendix D. Literature Flow Diagram for Guiding Question 3



*Other sources include references lists, referrals from experts, and grey literature searches.
†Five trials were used as sources for the models and were also included for Guiding Question 3.
MAT=medication-assisted treatment for opioid use disorder.

Appendix E. Included Studies List

Trials

Carrieri PM, Michel L, Lions C, et al. Methadone induction in primary care for opioid dependence: a pragmatic randomized trial (ANRS Methaville). PLoS ONE. 2014;9(11):e112328. PMID: 25393311.

Christensen DR, Landes RD, Jackson L, et al. Adding an Internet-delivered treatment to an efficacious treatment package for opioid dependence. J Consult Clin Psychol. 2014;82(6):964-72. PMID: 25090043.

D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. JAMA. 2015;313(16):1636-44. PMID: 25919527.

Fiellin DA, O'Connor PG, Chawarski M, et al. Methadone maintenance in primary care: a randomized controlled trial. JAMA. 2001;286(14):1724-31. PMID: 11594897.

Fiellin DA, Pantalon MV, Pakes JP, et al. Treatment of heroin dependence with buprenorphine in primary care. Am J Drug Alcohol Abuse. 2002;28(2):231-41. PMID: 12014814.

Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Engl J Med. 2006;355(4):365-74. PMID: 16870915.

Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. Am J Med. 2013;126(1):74.e11-7. PMID: 23260506.

Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003;349(10):949-58. PMID: 12954743.

Galanter M, Dermatis H, Glickman L, et al. Network therapy: decreased secondary opioid use during buprenorphine maintenance. J Subst Abuse Treat. 2004;26(4):313-8. PMID: 15182896.

King VL, Kidorf MS, Stoller KB, et al. A 12-month controlled trial of methadone medical maintenance integrated into an adaptive treatment model. J Subst Abuse Treat. 2006;31(4):385-93. PMID: 17084792.

Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. JAMA Intern Med. 2014;174(8):1369-76. PMID: 25090173.

Lintzeris N, Ritter A, Panjari M, et al. Implementing buprenorphine treatment in community settings in Australia: experiences from the Buprenorphine Implementation Trial. Am J Addict. 2004;13 Suppl 1:S29-41. PMID: 15204674.

Lucas GM, Chaudhry A, Hsu J, et al. Clinic-based treatment of opioid-dependent HIV-infected patients versus referral to an opioid treatment program: A randomized trial. Ann Intern Med. 2010;152(11):704-11. PMID: 20513828.

Moore BA, Barry DT, Sullivan LE, et al. Counseling and directly observed medication for primary care buprenorphine maintenance: a pilot study. J Addict Med. 2012;6(3):205-11. PMID: 22614936.

Roux P, Michel L, Cohen J, et al. Methadone induction in primary care (ANRS-Methaville): a phase III randomized intervention trial. BMC Public Health. 2012;12:488. PMID: 22741944. (pilot study to Carrieri et al, 2014)

Sullivan LE, Barry D, Moore BA, et al. A trial of integrated buprenorphine/naloxone and HIV clinical care. Clin Infect Dis. 2006;43 Suppl 4:S184-90. PMID: 17109305.

Tetrault JM, Moore BA, Barry DT, et al. Brief versus extended counseling along with buprenorphine/naloxone for HIV-infected opioid dependent patients. J Subst Abuse Treat. 2012;43(4):433-9. PMID: 22938914.

Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry. 2011;68(12):1238-46. PMID: 22065255.

Weiss RD, Potter JS, Griffin ML, et al. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. Drug Alcohol Depend. 2015;150:112-9. PMID: 25818060

Systematic Reviews

Amato L, Minozzi S, Davoli M, et al. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database Syst Rev. 2011(10):CD004147. PMID: 21975742.

Ferri M, Minozzi S, Bo A, et al. Slow-release oral morphine as maintenance therapy for opioid dependence. Cochrane Database Syst Rev. 2013;6:Cd009879. PMID: 23740540.

Gowing L, Farrell MF, Bornemann R, et al. Oral substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst Rev. 2011(8):Cd004145. PMID: 21833948.

Lobmaier P, Kornor H, Kunoe N, et al. Sustained-release naltrexone for opioid dependence. Cochrane Database Syst Rev. 2008(2):CD006140. PMID: 18425938.

Mattick RP, Breen C, Kimber J, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009(3):CD002209. PMID: 19588333.

Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;2:CD002207. PMID: 24500948.

Minozzi S, Amato L, Davoli M. Maintenance treatments for opiate dependent adolescent. Cochrane Database Syst Rev. 2009(2):CD007210. PMID: 19370679.

Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev. 2011(4):Cd001333. PMID: 21491383.

Minozzi S, Amato L, Bellisario C, et al. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev. 2013;12:CD006318. PMID: 24366859.

Rahimi-Movaghar A, Amin-Esmaeili M, Hefazi M, et al. Pharmacological therapies for maintenance treatments of opium dependence. Cochrane Database Syst Rev. 2013;1:Cd007775. PMID: 23440817.

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Appendix F. Excluded Studies List

Counseling Conditons for Thrice Weekly BUP in a PCC. PMID: SN029405. Excluded for not a study/systematic review.

Opiate Dependence: Combined Naltrexone/behavior Therapy. PMID: SN097696. Excluded for not a study/systematic review.

Buprenorphine combined with counseling found effective in reducing relapse. Alcoholism & Drug Abuse Weekly. 2003;3(10). PMID: 106876227. Excluded for not a study/systematic review.

Aalto M, Visapaa JP, Halme JT, et al. Effectiveness of buprenorphine maintenance treatment as compared to a syringe exchange program among buprenorphine misusing opioid-dependent patients. Nord J Psychiatry. 2011;65(4):238-43. PMID: 21047194. Excluded for wrong study design for Key Question.

Ahamad K, Milloy MJ, Nguyen P, et al. Factors associated with willingness to take extended release naltrexone among injection drug users. Addict Sci Clin Pract. 2015;10:12. PMID: 25935714. Excluded for wrong outcome.

Allen MA, Jewers H, McDonald JS. A Framework for the Treatment of Pain and Addiction in the Emergency Department. JEN. 2014;40(6). PMID: 103858648. Excluded for wrong intervention.

Amass L, Pukeleviciene V, Subata E, et al. A prospective, randomized, multicenter acceptability and safety study of direct buprenorphine/naloxone induction in heroin-dependent individuals. Addiction. 2012;107(1):142-51. PMID: 21749526. Excluded for drugs only.

Amato L, Davoli M, Minozzi S, et al. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev. 2013;2:Cd003409. PMID: 23450540. Excluded for wrong intervention.

Amato L, Minozzi S, Davoli M, et al. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database Syst Rev. 2011(9):CD005031. PMID: 21901695. Excluded for wrong intervention.

Amato L, Minozzi S, Davoli M, et al. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database Syst Rev. 2004(4):CD004147. PMID: 15495081. Excluded as a study covered by a systematic review.

Anonymous. Treatment of opiate dependence in hands of primary care providers. Public Health Rep. 2003;118(1):76. PMID: 12622131. Excluded for not a study/systematic review.

Anonymous. Public policy statement on Office-Based Opioid Agonist Treatment (OBOT). J Addict Dis. 2005;24(3):153-61. PMID: 16186090. Excluded for not a study/systematic review.

Apelt SM, Scherbaum N, Golz J, et al. Safety, effectiveness and tolerance of buprenorphine-naloxone in the treatment of opioid dependence: results from a nationwide non-interventional study in routine care. Pharmacopsychiatry. 2013;46(3):94-107. PMID: 23293011. Excluded for wrong study design for Key Question.

Aszalos R, McDuff DR, Weintraub E, et al. Engaging hospitalized heroin-dependent patients into substance abuse treatment. J Subst Abuse Treat. 1999;17(1-2):149-58. PMID: 10435263. Excluded for wrong study design for Key Question.

Barnett PG, Masson CL, Sorensen JL, et al. Linking opioid-dependent hospital patients to drug treatment: Health care use and costs 6 months after randomization. Addiction. 2006;101(12):1797-804. PMID: 17156179. Excluded for wrong setting.

Barry DT, Moore BA, Pantalon MV, et al. Patient satisfaction with primary care office-based buprenorphine/naloxone treatment. J Gen Intern Med. 2007;22(2):242-5. PMID: 17356993. Excluded for wrong outcome.

Berger R, Pulido C, Lacro J, et al. Group medication management for buprenorphine/naloxone in opioid-dependent veterans. J Addict Med. 2014;8(6):415-20. PMID: 25275875. Excluded for wrong study design for Key Question.

Bonhomme J, Shim RS, Gooden R, et al. Opioid addiction and abuse in primary care practice: a comparison of methadone and buprenorphine as treatment options. J Natl Med Assoc. 2012;104(7-8):342-50. PMID: 23092049. Excluded as a study covered by a systematic review.

Brands B, Blake J, Marsh D. Changing patient characteristics with increased methadone maintenance availability. Drug Alcohol Depend. 2002;66(1):11-20. PMID: 11850131. Excluded for wrong intervention.

Bryson WC, McConnell J, Korthuis PT, et al. Extended-release naltrexone for alcohol dependence: persistence and healthcare costs and utilization. Am J Manag Care. 2011;17 Suppl 8:S222-34. PMID: 21761949. Excluded for wrong study design for Key Question.

Burns L, Mattick RP, Lim K, et al. Methadone in pregnancy: treatment retention and neonatal outcomes. Addiction. 2007;102(2):264-70. PMID: 17222281. Excluded for wrong study design for Key Question.

Caldiero RM, Parran TV, Jr., Adelman CL, et al. Inpatient initiation of buprenorphine maintenance vs. detoxification: can retention of opioid-dependent patients in outpatient counseling be improved? Am J Addict. 2006;15(1):1-7. PMID: 16449087. Excluded for wrong study design for Key Question.

Carroll KM, Ball SA, Martino S, et al. Computer-assisted delivery of cognitive-behavioral therapy for addiction: a randomized trial of CBT4CBT. Am J Psychiatry. 2008;165(7):881-8. PMID: 18450927. Excluded for wrong population.

Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. SAMHSA/CSAT Treatment Improvement Protocol (TIP) Series, No. 43. HHS Publication No. (SMA) 12-4214. Rockville, MD. 2005. PMID: 22514849. Excluded for wrong setting.

Chawarski MC, Mazlan M, Schottenfeld RS. Behavioral drug and HIV risk reduction counseling (BDRC) with abstinence-contingent take-home buprenorphine: a pilot randomized clinical trial. Drug Alcohol Depend. 2008;94(1-3):281-4. PMID: 18164145. Excluded as a study covered by a systematic review.

Cheever LW, Kresina TF, Cajina A, et al. A model federal collaborative to increase patient access to buprenorphine treatment in HIV primary care. J Acquir Immune Defic Syndr. 2011;56 Suppl 1:S3-6. PMID: 21317591. Excluded as a study covered by a systematic review.

Chua SM, Lee TS. Abuse of prescription buprenorphine, regulatory controls and the role of the primary physician. Ann Acad Med Singapore. 2006;35(7):492-5. PMID: 16902726. Excluded as a study covered by a systematic review.

Clay E, Khemiri A, Zah V, et al. Persistence and healthcare utilization associated with the use of buprenorphine/naloxone film and tablet formulation therapy in adults with opioid dependence. J Med Econ. 2014;17(9):626-36. PMID: 24841329. Excluded for wrong study design for Key Question.

Colameco S, Armando J, Trotz C. Opiate dependence treatment with buprenorphine: one year's experience in a family practice residency setting. J Addict Dis. 2005;24(2):25-32. PMID: 15784521. Excluded for wrong study design for Key Question.

Colson J, Helm S, Silverman SM. Office-based opioid dependence treatment. Pain physician. 2012;15(3 Suppl):ES231-6. PMID: 22786460. Excluded as a study covered by a systematic review.

Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. Harv Rev Psychiatry. 2015;23(2):63-75. PMID: 25747920. Excluded as a study covered by a systematic review.

Copenhaver MM, Bruce RD, Altice FL. Behavioral counseling content for optimizing the use of buprenorphine for treatment of opioid dependence in community-based settings: a review of the empirical evidence. Am J Drug Alcohol Abuse. 2007;33(5):643-54. PMID: 17891657. Excluded as a study covered by a systematic review.

Cozzolino E, Guglielmino L, Vigezzi P, et al. Buprenorphine treatment: a three-year prospective study in opioid-addicted patients of a public out-patient addiction center in Milan. Am J Addict. 2006;15(3):246-51. PMID: 16923672. Excluded for wrong setting.

Cunningham C, Giovanniello A, Sacajiu G, et al. Buprenorphine treatment in an urban community health center: what to expect. Fam Med. 2008;40(7):500-6. PMID: 18928077. Excluded for drugs only.

Cunningham CO, Giovanniello A, Li X, et al. A comparison of buprenorphine induction strategies: patient-centered home-based inductions versus standard-of-care office-based inductions. J Subst Abuse Treat. 2011;40(4):349-56. PMID: 21310583. Excluded for wrong study design for Key Question.

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Daniels AM, Salisbury-Afshar E, Hoffberg A, et al. A novel community-based buprenorphine program: client description and initial outcomes. J Addict Med. 2014;8(1):40-6. PMID: 24394496. Excluded for wrong setting.

Davies D. Buprenorphine versus methadone--safety first? Br J Gen Pract. 2005;55(512):232-3. PMID: 15808047. Excluded for not a study/systematic review.

De Ducla M, Gagnon A, Mucchielli A, et al. Comparison of high dose buprenorphine treatments of opiate dependent outpatients in four healthcare networks. Ann Med Interne (Paris). 2000;151 Suppl B:B9-15. PMID: 11104938. Excluded for wrong study design for Key Question.

DeFulio A, Everly JJ, Leoutsakos JM, et al. Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial. Drug Alcohol Depend. 2012;120(1-3):48-54. PMID: 21782353. Excluded for wrong setting.

Donaher PA, Welsh C. Managing opioid addiction with buprenorphine. Am Fam Physician. 2006;73(9):1573-8. PMID: 16719249. Excluded as a study covered by a systematic review.

Doolittle B, Becker W. A case series of buprenorphine/naloxone treatment in a primary care practice. Substance abuse. 2011;32(4):262-5. PMID: 22014257. Excluded for drugs only.

Drainoni ML, Farrell C, Sorensen-Alawad A, et al. Patient perspectives of an integrated program of medical care and substance use treatment. AIDS Patient Care STDS. 2014;28(2):71-81. PMID: 24428768. Excluded for wrong study design for Key Question.

Ducharme S, Fraser R, Gill K. Update on the clinical use of buprenorphine: in opioid-related disorders. Can Fam Physician. 2012;58(1):37-41. PMID: 22267618. Excluded as a study covered by a systematic review.

Egan JE, Netherland J, Gass J, et al. Patient perspectives on buprenorphine/naloxone treatment in the context of HIV care. Jo Acquir Immune Defic Syndr. 2011;56 Suppl 1:S46-53. PMID: 21317594. Excluded for wrong study design for Key Question.

Everly JJ, DeFulio A, Koffarnus MN, et al. Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: a randomized controlled trial. Addiction. 2011;106(7):1309-18. PMID: 21320227. Excluded for wrong setting.

Fals-Stewart W, O'Farrell TJ. Behavioral family counseling and naltrexone for male opioid-dependent patients. J Consult Clin Psychol. 2003;71(3):432-42. PMID: 12795568. Excluded for wrong setting.

Fareed A, Eilender P, Ketchen B, et al. Factors affecting noncompliance with buprenorphine maintenance treatment. J Addict Med. 2014;8(5):345-50. PMID: 25072677. Excluded for wrong study design for Key Question.

Fareed A, Vayalapalli S, Casarella J, et al. Treatment outcome for flexible dosing buprenorphine maintenance treatment. Am J Drug Alcohol Abuse. 2012;38(2):155-60. PMID: 22175698. Excluded for drugs only.

Ferner RE, Daniels AM. Office-based treatment of opioid-dependent patients. N Engl J Med. 2003;348(1):81-2; author reply -2. PMID: 12510051. Excluded for not a study/systematic review.

Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. Cochrane Database Syst Rev. 2011(12):Cd003410. PMID: 22161378. Excluded for wrong intervention.

Ferri M, Finlayson AJ, Wang L, et al. Predictive factors for relapse in patients on buprenorphine maintenance. Am J Addict. 2014;23(1):62-7. PMID: 24313243. Excluded for wrong setting.

Fiellin DA. Buprenorphine: effective treatment of opioid addiction starts in the office. Am Fam Physician. 2006;73(9):1513-4. PMID: 16719242. Excluded as a study covered by a systematic review.

Fiellin DA, O'Connor PG. Office-Based Treatment of Opioid-Dependent Patients. PMID: 7298856. Excluded for not a study/systematic review.

Fiellin DA, O'Connor PG. Clinical practice Office-based treatment of opioid-dependent patients. N Engl J Med. 2002;9(12). PMID: 106819223. Excluded for not a study/systematic review.

Fiellin DA, O'Connor PG, Chawarski M, et al. Processes of care during a randomized trial of office-based treatment of opioid dependence in primary care. Am J Addict. 2004;13 Suppl 1:S67-78. PMID: 15204676. Excluded for wrong study design for Key Question.

Fiellin DA, Schottenfeld RS, Cutter CJ, et al. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern Med. 2014;174(12):1947-54. PMID: 25330017. Excluded for drugs only.

Fingerhood MI, King VL, Brooner RK, et al. A comparison of characteristics and outcomes of opioid-dependent patients initiating office-based buprenorphine or methadone maintenance treatment. Substance abuse. 2014;35(2):122-6. PMID: 24821346. Excluded for wrong study design for Key Question.

Fischer G, Etzersdorfer P, Eder H, et al. Buprenorphine maintenance in pregnant opiate addicts. Eur Addict Res. 1998;4 Suppl 1:32-6. PMID: 9767205. Excluded for wrong study design for Key Question.

Fischer G, Johnson RE, Eder H, et al. Treatment of opioid-dependent pregnant women with buprenorphine. Addiction. 2000;95(2):239-44. PMID: 10723852. Excluded for drugs only.

Fischer G, Ortner R, Rohrmeister K, et al. Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. Addiction. 2006;101(2):275-81. PMID: 16445556. Excluded for wrong setting.

Fishman MJ, Winstanley EL, Curran E, et al. Treatment of opioid dependence in adolescents and young adults with extended release naltrexone: preliminary case-series and feasibility. Addiction. 2010;105(9):1669-76. PMID: 20626723. Excluded for wrong study design for Key Question.

French MT. Cost-effectiveness of buprenorphine maintenance versus methadone maintenance. Addiction. 2001;96(10):1515-7. PMID: 11599513. Excluded as a study covered by a systematic review.

George S. Review: methadone increases retention and reduces heroin use compared with non-pharmacological maintenance. Evidence Based Mental Health. 2010;13(1). PMID: 105126642. Excluded for not a study/systematic review.

Giacomuzzi SM, Riemer Y, Ertl M, et al. Buprenorphine versus methadone maintenance treatment in an ambulant setting: a health-related quality of life assessment. Addiction. 2003;98(5):693-702. PMID: 12751987. Excluded for wrong study design for Key Question.

Gordon AJ, Trafton JA, Saxon AJ, et al. Implementation of buprenorphine in the Veterans Health Administration: results of the first 3 years. Drug Alcohol Depend. 2007;90(2-3):292-6. PMID: 17493771. Excluded for wrong outcome.

Gorelick DAEAdinng. Counseling plus Buprenorphine-Naloxone for Opioid Dependence. 2006. PMID: 22754101. Excluded for not a study/systematic review.

Gossop M, Marsden J, Stewart D, et al. The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. Addiction. 2003;98(3):291-303. PMID: 12603229. Excluded for wrong study design for Key Question.

Gossop M, Marsden J, Stewart D, et al. Methadone treatment practices and outcome for opiate addicts treated in drug clinics and in general practice: results from the National Treatment Outcome Research Study. Br J Gen Pract. 1999;49(438):31-4. PMID: 10622013. Excluded for wrong study design for Key Question.

Gossop M, Stewart D, Browne N, et al. Methadone treatment for opiate dependent patients in general practice and specialist clinic settings: Outcomes at 2-year follow-up. J Subst Abuse Treat. 2003;24(4):313-21. PMID: 12867205. Excluded for wrong study design for Key Question.

Gourevitch MN, Chatterji P, Deb N, et al. On-site medical care in methadone maintenance: associations with health care use and expenditures. J Subst Abuse Treat. 2007;32(2):143-51. PMID: 17306723. Excluded for wrong study design for Key Question.

Haddad MS, Zelenev A, Altice FL. Integrating buprenorphine maintenance therapy into federally qualified health centers: real-world substance abuse treatment outcomes. Drug Alcohol Depend. 2013;131(1-2):127-35. PMID: 23332439. Excluded for wrong study design for Key Question.

Haddad MS, Zelenev A, Altice FL. Buprenorphine maintenance treatment retention improves nationally recommended preventive primary care screenings when integrated into urban federally qualified health centers. J Urban Health. 2015;92(1):193-213. PMID: 25550126. Excluded for wrong study design for Key Question.

Herman M, Gourevitch MN. Integrating primary care and methadone maintenance treatment: implementation issues. J Addict Dis. 1997;16(1):91-102. PMID: 9046446. Excluded as a study covered by a systematic review.

Hersh D, Little SL, Gleghorn A. Integrating buprenorphine treatment into a public healthcare system: the San Francisco Department of Public Health's office-based Buprenorphine Pilot Program. J Psychoactive Drugs. 2011;43(2):136-45. PMID: 21858959. Excluded for wrong study design for Key Question.

Hulse GK. Subcutaneous naltrexone implants reduce opioid use in opiate dependent patients. Evid Based Ment Health. 2010;13(1):25. PMID: 105126640. Excluded for not a study/systematic review.

Hulse GK, Morris N, Arnold-Reed D, et al. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. Arch Gen Psychiatry. 2009;66(10):1108-15. PMID: 19805701. Excluded as a study covered by a systematic review.

Hulse GK, O'Neil G, Arnold-Reed DE. Methadone maintenance vs. implantable naltrexone treatment in the pregnant heroin user. Int J Gynaecol Obstet. 2004;85(2):170-1. PMID: 15099783. Excluded for wrong study design for Key Question.

Hulse GK, Tait RJ, Comer SD, et al. Reducing hospital presentations for opioid overdose in patients treated with sustained release naltrexone implants. Drug Alcohol Depend. 2005;79(3):351-7. PMID: 15899557. Excluded as a study covered by a systematic review.

Imani S, Vahid MKA, Gharraee B, et al. Comparing mindfulness-based group therapy with treatment as usual for opioid dependents: A pilot randomized clinical trial study protocol. Iran J Psychiatry Behav Sci. 2015;9(1):1-4. Excluded for not a study/systematic review.

King VL, Burke C, Stoller KB, et al. Implementing methadone medical maintenance in community-based clinics: disseminating evidence-based treatment. J Subst Abuse Treat. 2008;35(3). PMID: 105572046. Excluded for wrong setting.

King VL, Stoller KB, Hayes M, et al. A multicenter randomized evaluation of methadone medical maintenance. Drug Alcohol Depend. 2002;65(2):137-48. PMID: 11772475. Excluded as a study covered by a systematic review.

Kouimtsidis C, Reynolds M, Coulton S, et al. How does cognitive behaviour therapy work with opioid-dependent clients? Results of the UKCBTMM Study. Drugs: Educ Prev Polic. 2012;19(3):253-8. PMID: 2012-10430-009.Exclusion Code:4.

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Krupitsky E, Nunes EV, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011;377(9776):1506-13. PMID: 21529928. Excluded for drugs only.

Krupitsky E, Zvartau E, Blokhina E, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. Arch Gen Psychiatry. 2012;69(9):973-81. PMID: 22945623. Excluded as a study covered by a systematic review.

Kuhn S, Schu M, Vogt I, et al. Psychosocial care in the German model project on heroin-maintenance therapy for opiate dependence. [German]. Sucht. 2007;53(5):278-87. Excluded for not English language.

Kunoe N, Lobmaier P, Vederhus JK, et al. Challenges to antagonist blockade during sustained-release naltrexone treatment. Addiction. 2010;105(9):1633-9. PMID: 20707781. Excluded for wrong study design for Key Question.

Kunoe N, Lobmaier P, Vederhus JK, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. Br J Psychiatry. 2009;194(6):541-6. PMID: 19478295. Excluded for wrong setting.

Kunoe N, Lobmaier P, Vederhus JK, et al. Retention in naltrexone implant treatment for opioid dependence. Drug Alcohol Depend. 2010;111(1-2):166-9. PMID: 20570059. Excluded for wrong study design for Key Question.

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Appendix G. Details of Trials for Guiding Question 3

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
MAT Models of Care								
D'Onofrio, 2015[1]	Screening and referral to treatment (referral) vs. screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention) vs. screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine)	30 days	329	USA; 76.3% male; 75.4% white; mean age 31.4 years (SD 10.6); study done in USA; 34.3% use alcohol to intoxication; 47.4% used sedatives in past month; 52.9% used cannabis in past month; 55.3% used cocaine in past month; 88.1% used cigarettes in past month; 51.1% had received psychiatric treatment in the past; 26.1% had received in-patient psychiatric treatment; 41.9% had received out-patient psychiatric treatment; 12.2% had received treatment for depression in the past month; 24.9% used prescription opioids; 75.1% used heroin; 52.9% were IV drug users	Buprenorphine group given treatment for 10 weeks before transferred to community program or detoxification for 2 weeks; Referral group received information for treatment programs only; brief intervention program received a brief 10- to 15-minute manual-driven audio-taped brief negotiation interview from a research associate who linked them with a referral; buprenorphine group received a Brief Negotiation Interview and if they exhibited moderate to severe opioid withdrawal received ED-initiated treatment and sufficient take-home daily doses to get through to next appointment, those without opioid withdrawal were given unobserved inducted with detailed self-medication guide, then office based buprenorphine treatment, and ongoing opioid agonist maintenance treatment or detoxification	Urban teaching hospital; Research associate performed ED visits, interviews, and referrals. Physicians and nurses managed buprenorphine dosages	Engagement in treatment assessed by direct contact with the facility, clinicians, or both; self-reported number of days of illicit opioids use in the past 7 days; urine toxicology for illicit opioid use; HIV risk-taking behavior using an 11-item validated scale for drug use and sexual behavior; and use of addiction treatment services.	Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk. These findings require replication in other centers before widespread adoption.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2002[2]	Buprenorphine and medication management (thrice-weekly sessions with a nurse and a monthly meeting with a physician) vs. buprenorphine and medication management plus drug counseling (not described)	13 weeks	14	USA; 71% male; 93% white, mean age 36 years; 50% current IV drug user; mean 7 years heroin use; 79% with history/current alcohol dependence; 79% with history/current cocaine dependence	Buprenorphine given 3 times per week following one week induction with dose escalation as needed for positive urine screen or withdrawal. Medication management group had brief monthly counseling sessions with physicians and 3 times per week manual-guided counseling sessions with nurses covering recent drug use, abstinence efforts, attendance at self-help groups with support and advice for efforts to reduce drug use or remain abstinent. Medication management plus manual-guided drug counseling sessions met weekly (no details provided)	Urban academically affiliated medical center; primary care; medical management provided by nurses and physicians (counseling issues reviewed weekly with physician and clinical psychologist)	Illicit drug use: urine toxicology and self report Retention/adherence: attendance at visits Overall health:SF-36 Patient satisfaction	Overall, patients reduced opioid-positive urine toxicology tests and good retention through maintenance; less patients in medication management group vs. medication management plus counseling group achieved greater than or equal to one week of opioid-free urine screens, though this difference was not statistically significant; A greater proportion of the medication management plus counseling group had opioid-free urine screens compared with the medication management alone group, though this difference was not statistically significant

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2006[3]	Standard medical management (20 minutes with a nurse) and once-weekly medication dispensing (buprenorphine-naloxone) vs. standard medical management and thrice-weekly medication dispensing vs. enhanced (45 minutes with a nurse) medical management and thrice-weekly medication dispensing All groups met monthly with a physician	24 weeks	166	USA; 78% male; 77% white; mean age 36 years; mean duration of opioid dependence 8 years; 17% prescription drug use; 31% history of intravenous drug use; 20% cocaine-positive urine specimen at treatment entry; 66% previously attempted detoxification; 32% history of participation in methadone-maintenance program	Nurses dispensed buprenorphine-naloxone and provided standard (20 minutes; sessions covered recent drug use or efforts to achieve or maintain abstinence, attendance in self-help groups, support for efforts to reduce drug use or remain abstinent, advice for the achievement or maintenance of abstinence, and the results of analysis of weekly urine specimens) or enhanced (45 minutes; sessions covered similar issues but provided more in-depth drug counseling) medical management Physicians met with patients monthly (20 minutes; sessions paralleled that of the standard sessions, with the addition of an assessment of employment, legal, family or social, medical, and psychiatric problems related to addiction) The nurses, a physician, and a psychologist met weekly to review the counseling	Trained primary care nurses without previous addiction treatment, physician, psychologist Primary care center	Illicit opioid use: urine toxicology and self-report Abstinence: measured in consecutive weeks	The efficacy of brief weekly counseling and once-weekly medication dispensing did not differ significantly from that of extended weekly counseling and thrice-weekly dispensing
Liebschutz, 2014[4]	Detoxification plus referral vs. induction plus contact from long-term opioid agonist treatment staff that facilitated linkage to hospital-associated primary care buprenorphine treatment	6 months	139	USA; 71.2% male; mean age 40.5 (SD 11.8); mean illicit opioid use per 30 followup days 20.8 (SD 9.7)	Both groups received buprenorphine and naloxone up to 4 times for the first day in the hospital. Detoxification group received 4 additional days of tapering buprenorphine and naloxone, then treatment referral information; linkage group received buprenorphine and naloxone for hospitalization with enough given at discharge to get through to clinic appointment, before discharge research staff facilitated linkage to hospital-associated primary care buprenorphine treatment	Hospital and medical center; Research staff, which included an addiction nurse specialist, hospital nursing staff administered medication in hospital	Entry into opioid agonist treatment program, length of illicit opioid use defined as number of days of reported opioid use in the 30 days before visits, time to entry into buprenorphine program, number of self-reported prescribed opioid agonist treatment in the 30 days before visits, mortality.	Compared with an inpatient detoxification protocol, initiation of and linkage to buprenorphine treatment is an effective means for engaging medically hospitalized patients who are not seeking addiction treatment and reduces illicit opioid use 6 months after hospitalization. However, maintaining engagement in treatment remains a challenge.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Lucas, 2010[5]	Clinic-based, nurse-administered treatment with buprenorphine-naloxone vs. case management and referral to an intensive opioid treatment program (referred treatment)	12 months	93	USA; 72% male; 98% black; median ages 45-46 years; median years of opioid use 18-20 years; 96% heroin used in previous month; 27% prescription opioid used in previous month; 72% used cocaine in previous month; 60% injection drug use in previous month; 73% positive for hepatitis C antibody; 10% AIDS-defining opportunistic condition in previous 3 months; 53% receiving ART	Clinic-based group was managed and seen weekly by a nurse (10-40 minutes; sessions included unstructured individual counseling, urine samples, observed buprenorphine doses, and provision of take-home supplies of buprenorphine to last until their next visit), and met with a physician 4-6 weeks after initiation of therapy and at other times as indicated. A treatment team, comprising the nurse and 2 to 5 buprenorphine prescribing physicians, met weekly to discuss participants' progress in treatment. The treatment team set reporting frequencies, which ranged from 3 times weekly to monthly, according to drug test results and other factors. Participants assigned to referred treatment were enrolled in an intensive case management program that has operated in the same clinic. A social worker or registered nurse in the case management program met with referred treatment participants shortly after randomization and made treatment plans that were primarily focused on linking participants to opioid treatment programs, but may have included such issues as food and housing needs	Licensed practical nurse with training and experience as a substance counselor, buprenorphine prescribing physicians HIV clinic	Drug use: urine toxicology Participation in opioid agonist therapy at study visits: self-reported Also, visits with primary HIV providers, months of ART use, changes in HIV RNA levels and CD4 cell counts, and proportion of participants with emergency department visits or hospitalizations (methods NR)	Participation in opioid agonist therapy was significantly higher in clinic-based buprenorphine than for referred treatment. Positive test results for opioids and cocaine were significantly less frequent in clinic-based buprenorphine than in referred treatment, and study participants receiving clinic-based buprenorphine attended significantly more HIV primary care visits than those receiving referred treatment. Use of antiretroviral therapy and changes in HIV RNA levels and CD4 cell counts did not differ between the 2 groups.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Sullivan, 2006[6]	Buprenorphine/ naloxone and physician management (brief, biweekly) vs. buprenorphine/ naloxone and physician management plus once-weekly drug counseling and adherence management	12 weeks	16	USA; 94% male; 31% white, 44% Black, 25% Hispanic; mean age 47 years; mean 17 years opioid dependence; 56% with injection drug use; 29% reported one or more days of alcohol use in past 30 days; 36% reported one or more days of cocaine use in past 30 days; 100% HIV positive; mean 13 years since HIV diagnosis; 63% currently on ART; 81% HCV positive	Buprenorphine/naloxone stabilization over 2-weeks with clinic visits 3 times per week and 1 and 2-day take home doses then 10-week maintenance period with once weekly clinic visits and 6 take home doses then offered 2-week taper or extension phase; all patients received brief, bi-weekly, manual-guided physician management that focused on symptoms, drug use, and progress; half of patients received physician management plus once-weekly drug counseling and adherence management focused on addiction-specific topics like triggers, relationships, and craving and strategies to increased adherence to antiretroviral treatment	HIV clinics; Buprenorphine and physician managment provided by physician specialized in addiction medicine and experienced in HIV care; drug counseling and adherence management provided by trained nursing staff (issues reviewed with supervising physician and clinical psychologist)	Treatment retention Illicit drug use: urine toxicology and self-report Laboratory parameters: CD4 count, viral load, and liver function tests Adherence to MAT and ART: Medication Event Monitoring System (caps that record the date and time the pill bottle was opened) HIV transmission risk behaviors: HIV/AIDS Risk Inventory Health status: SF-36 Patient satisfaction: 5-point Likert scale questionnaire	There was no difference in treatment retention or illicit drug use by counseling group; Overall, the proportion of opioid-positive weekly urine screens decreased substantially over trial; CD4 counts remained stable; viral load declined significantly; demonstrated feasibility of integrating buprenorphine into HIV clinical care for treatment of opioid dependence
Psychosocial Interventions								
Christensen, 2014[7]	Buprenorphine and individual counseling plus contingency management (based on urine results linked to points for gift cards or money) vs. buprenorphine and individual counseling and contingency management plus internet-based community reinforcement approach Both groups had individual counseling every 2 weeks	12 weeks	170	USA; 54% male, 95% white, mean age 34 years; 13% with concurrent alcohol dependence, 5% with concurrent cocaine dependence, 12% with concurrent sedative dependence, 29% with concurrent cannabis dependence; 46% had prior treatment; 14% with injection drug use	Buprenorphine given 3 times per week with extra dose for days in between; contingency management based on urine results linked to points for gift cards or money; community reinforcement approach completed set of topics on community reinforcement approach at each clinic visit; both groups had individual counseling every 2 weeks	Clinic setting at university research center; Buprenorphine from study physician; therapist for community reinforcement approach and counseling	Retention: number of days from start of intervention until participant left trial or completed trial Abstinence: number of negative urine specimens overall and over longest continuous period with missed visits equal to positive result Addiction-related severity: ASI	Compared to those receiving contingency management-alone, community reinforcement approach recipients had more total days of abstinence and were less likely to drop out of treatment; prior treatment for opioid dependence moderated the additional improvement of community reinforcement approach for longest continuous days of abstinence

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2002[2] (also a model of care	Buprenorphine and medication management (thrice-weekly sessions with a nurse and a monthly meeting with a physician) vs. buprenorphine and medication management plus drug counseling (not described)	13 weeks	14	USA; 71% male; 93% white, mean age 36 years; 50% current IV drug user; mean 7 years heroin use; 79% with history/current alcohol dependence; 79% with history/current cocaine dependence	Buprenorphine given 3 times per week following one week induction with dose escalation as needed for positive urine screen or withdrawal. Medication management group had brief monthly counseling sessions with physicians and 3 times per week manual-guided counseling sessions with nurses covering recent drug use, abstinence efforts, attendance at self-help groups with support and advice for efforts to reduce drug use or remain abstinent. Medication management plus manual-guided drug counseling sessions met weekly (no details provided)	Urban academically affiliated medical center; primary care; medical management provided by nurses and physicians (counseling issues reviewed weekly with physician and clinical psychologist)	Illicit drug use: urine toxicology and self report Retention/adherence: attendance at visits Overall health:SF-36 Patient satisfaction	Overall, patients reduced opioid-positive urine toxicology tests and good retention through maintenance; less patients in medication management group vs. medication management plus counseling group achieved greater than or equal to one week of opioid-free urine screens, though this difference was not statistically significant; A greater proportion of the medication management plus counseling group had opioid-free urine screens compared with the medication management alone group, though this difference was not statistically significant

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2006[3] (also a model of care)	Standard medical management (20 minutes with a nurse) and once-weekly medication dispensing (buprenorphine-naloxone) vs. standard medical management and thrice-weekly medication dispensing vs. enhanced (45 minutes with a nurse) medical management and thrice-weekly medication dispensing All groups met monthly with a physician	24 weeks	166	USA; 78% male; 77% white; mean age 36 years; mean duration of opioid dependence 8 years; 17% prescription drug use; 31% history of intravenous drug use; 20% cocaine-positive urine specimen at treatment entry; 66% previously attempted detoxification; 32% history of participation in methadone-maintenance program	Nurses dispensed buprenorphine-naloxone and provided standard (20 minutes; sessions covered recent drug use or efforts to achieve or maintain abstinence, attendance in self-help groups, support for efforts to reduce drug use or remain abstinent, advice for the achievement or maintenance of abstinence, and the results of analysis of weekly urine specimens) or enhanced (45 minutes; sessions covered similar issues but provided more in-depth drug counseling) medical management Physicians met with patients monthly (20 minutes; sessions paralleled that of the standard sessions, with the addition of an assessment of employment, legal, family or social, medical, and psychiatric problems related to addiction) The nurses, a physician, and a psychologist met weekly to review the counseling	Trained primary care nurses without previous addiction treatment, physician, psychologist Primary care center	Illicit opioid use: urine toxicology and self-report Abstinence: measured in consecutive weeks	The efficacy of brief weekly counseling and once-weekly medication dispensing did not differ significantly from that of extended weekly counseling and thrice-weekly dispensing

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2013[8]	Physician management (15-20 minutes weekly for the first 2 weeks, every 2 weeks for the next 4 weeks, and then monthly) with buprenorphine-naloxone or physician management with buprenorphine-naloxone plus CBT (up to 12 50-minute weekly sessions during the first 12 weeks of treatment)	24 weeks	141	USA; 74% male; 90% white; mean age 34 years; mean time opioid dependent 8 years; 35% prescription drug use; 32% current injection drug use; 45% prior attempted detoxification; 59% prior substance abuse treatment; mean 1.3 days of use of cocaine in previous 30 days	Physician management (15-20 minutes; sessions occurred weekly for the first 2 weeks, every 2 weeks for the next 4 weeks, and then monthly). The physician followed a structured note that reviewed the patient's recent drug use; provided brief advice on how to achieve or maintain abstinence; supported efforts to reduce drug use or remain abstinent; reviewed medical and psychiatric symptoms; assessed social, work, and legal function; discussed weekly urine toxicology results; and reviewed attendance at self-help groups.CBT was provided using a CBT manual adapted for cocaine dependence. Fidelity measures were taken and supervision provided. Patients were offered up to 12 50-minute weekly sessions during the first 12 weeks of treatment. The main components of counseling focused on performing a functional analysis of behavior, promoting behavioral activation, identifying and coping with drug cravings, enhancing drug-refusal skills, enhancing decision-making about high-risk situations, and improving problem-solving skills.	Internal medicine physicians with experience providing buprenorphine, trained masters and doctoral-level clinicians Primary care clinic	Frequency of illicit opioid use: self-report Maximum number ofconsecutive weeks of abstinence from illicit opioids: urine toxicology and self-report Also, the proportion of patients remaining in the study (the percentage of patients who did not meet the criteria for protective transfer, did not miss medication for 7 days, or did not miss 3 physician management sessions), the number of days of the study that were completed, and self-reported abstinence from cocaine use (verifiedby urinalysis)	The effectiveness of physician management did not differ significantly from that of physician management plus CBT.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Galanter, 2004[9]	Buprenorphine plus medication management (2 individual sessions per week) vs. buprenorphine plus network therapy (1 individual and 1 group counseling session per week)	18 weeks	66	USA; 76% male; 59% white, 24% Hispanic, 12% Black, 5% Asian/other; mean age 36 years; mean 12 years of heroin use; 33% had injection drug use in past 30 days; 73% had history of treatment for heroin addiction, 30% had history of methadone maintenance treatment	Patients underwent induction on buprenorphine/naloxone, maintenance phase, and taper off over 15 weeks, doses given daily aside for weekend take-home dosing Network therapy had one group and one individual session per week; Network therapy trains network members to provide supportive environment for patient's adherence to avoidance of illicit drug use, joint sessions with support network members as well as individual sessions organized; Medication management had two individual sessions per week; medication management focused on medication response and adherence monitoring and the establishment of therapeutic relationship	Office-based; Therapies provided by psychiatry resident physicians	Illicit drug use: urine toxicologies, percentage of negative screens (goal of adherence to abstinence expectation) and whether or not last 3 scheduled urines in study were negative (goal of opiate-free state by end of treatment)	Network therapy led to significantly more negative urine toxicologies and more network therapy than medication management patients had positive outcome relative to secondary heroin use by the end of treatment
Moore, 2012[10]	Buprenorphine and physician management (15 minute sessions weekly) vs. buprenorphine and physician management plus CBT (45 minute sessions weekly, depending on therapist availability)	12 weeks	55	France; 74% male; mean age 39 years; 72% white; mean opioid dependence 9 years; 45% prescription drug use; 16% history of IV drug use; 41% prior attempted detoxification	Physician management included weekly buprenorphine dispensing, 15 minutes per session Other arm included physician management and thrice weekly directly observed buprenorphine therapy plus weekly CBT, 45 minutes per session, based on therapist availability	Adult primary care center of an urban teaching hospital; Physician management provided by primary care internal medicine physician with experience in office-based buprenorphine treatment. CBT provided by trained therapists (2 master's level and 3 doctoral-level) with at least 3 years of experience. Induction performed by trained nursing staff.	Drug use: urine toxicology and self-report Treatment completion: continued participation through the 14th week; Treatment retention: number of weeks; Patient satisfaction: Primary Care Buprenorphine Satisfaction Scale	Analyses adjusting for baseline characteristics showed no significant differences between groups on retention or drug use based on self-report or urines. Patient satisfaction was high across conditions, indicating acceptability of CBT counseling with observed medication. The number of CBT sessions attended was significantly associated with improved outcome, and session attendance was associated with a greater abstinence the following week.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Sullivan, 2006[6] (also a model of care)	Buprenorphine/naloxone and physician management (brief, biweekly) vs. buprenorphine/naloxone and physician management plus once-weekly drug counseling and adherence management	12 weeks	16	USA; 94% male; 31% white, 44% Black, 25% Hispanic; mean age 47 years; mean 17 years opioid dependence; 56% with injection drug use; 29% reported one or more days of alcohol use in past 30 days; 36% reported one or more days of cocaine use in past 30 days; 100% HIV positive; mean 13 years since HIV diagnosis; 63% currently on ART; 81% HCV positive	Buprenorphine/naloxone stabilization over 2-weeks with clinic visits 3 times per week and 1 and 2-day take home doses then 10-week maintenance period with once weekly clinic visits and 6 take home doses then offered 2-week taper or extension phase; all patients received brief, bi-weekly, manual-guided physician management that focused on symptoms, drug use, and progress; half of patients received physician management plus once-weekly drug counseling and adherence management focused on addiction-specific topics like triggers, relationships, and craving and strategies to increased adherence to antiretroviral treatment	HIV clinics; Buprenorphine and physician managment provided by physician specialized in addiction medicine and experienced in HIV care; drug counseling and adherence management provided by trained nursing staff (issues reviewed with supervising physician and clinical psychologist)	Treatment retention Illicit drug use: urine toxicology and self-report Laboratory parameters: CD4 count, viral load, and liver function tests Adherence to MAT and ART: Medication Event Monitoring System (caps that record the date and time the pill bottle was opened) HIV transmission risk behaviors: HIV/AIDS Risk Inventory Health status: SF-36 Patient satisfaction: 5-point Likert scale questionnaire	There was no difference in treatment retention or illicit drug use by counseling group; Overall, the proportion of opioid-positive weekly urine screens decreased substantially over trial; CD4 counts remained stable; viral load declined significantly; demonstrated feasibility of integrating buprenorphine into HIV clinical care for treatment of opioid dependence

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Tetrault, 2012[11]	Physician management (brief, once every 2 weeks) vs. physician management plus enhanced medical management (45 minutes weekly; focused on drug counseling and adherence to anti-retroviral treatment)	12 weeks	47	USA; 39% male; 29% white; mean age 47 years; mean 4 days of alcohol use in past 30 days; mean 5 days of cocaine use in past 30 days; mean 17 years of opioid dependence; 87% with primary heroin use; 49% with injection drug use; mean 12 years duration of HIV diagnosis; 61% receiving ART, 26% HCV positive	Physician management group had physician visit once every 2 weeks where they took medication under observation and were given a supply to take-home; physician management was brief, manual-guided, medically focused counseling intervention that focused on drug use, symptoms, side effects. Enhanced medical management group had clinic weekly, took medication under observation, and given supply to take home; enhanced medical management was a manual-guided counseling intervention lasting 45 minutes focused on drug counseling and adherence to ART	HIV clinic; Physicians for medication and physician management; nurses delivered enhanced medical management	Illicit drug use: percentage of opioid-negative urine specimens, drug urine screen; and self-report Abstinence: self-report Study completion: not meeting criteria for protective transfer (3 consecutive positive urine tests after buprenorphine dose increased), continued research visits and medication dispensing through week 12 MAT and ART adherence: computerized bottle caps HIV clinical data: CD-4 and viral load HIV risk behaviors: AIDS Risk InventoryImpact of opioid treatment and counseling into HIV setting: buprenorphine/naloxone dose, number of sessions attended, length of visits, number of sessions missed	At end of trial, no difference between groups in percentage of opioid negative urines, maximum duration of continuous abstinence, or retention; the percentage of subjects with detectable viral loads decreased from baseline across both groups similarly; overall, providing extended counseling in this setting is feasible but does not provide detectable improvement in outcomes

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Weiss, 2011[12] Prescription Opioid Addiction Treatment Study (POATS)	Phase 1: Standard medication management (after initial session,15-20 minute s weekly, then biweekly sessions with a physician) with buprenorphine/ naloxone vs. standard medication management with buprenorphine/ naloxone plus opioid dependence counseling (45-60 minute sessions with a counselor, twice weekly then biweekly) Phase 2 (extended treatment for those who relapsed): Standard medication management (2 visits first week, then weekly) with buprenorphine/ naloxone vs. standard medication management with buprenorphine/ naloxone plus opioid dependence counseling (twice weekly then biweekly)	Phase 1: 12 weeks Phase 2 (for patients with unsuccessful outcomes): 24 weeks	653	USA; 60% male; 91% white; mean age 33 years; 27% alcohol dependence during lifetime; 18% cocaine dependence during lifetime; 5 mean years of opioid use; 23% used heroin ever; 32% previous treatment for OUD; 42% current chronic pain	Physicians provided manual-based, standard medical management. During the initial sessions (45-60 minutes in phase 1 and 30-60 minutes in phase 2), the physician reviewed the patient's medical, psychiatric, and substance use problems; recommended abstinence; and referred the patient to self-help groups. In subsequent visits (15-20 minutes), the physician assessed substance use, craving, and buprenorphine-naloxone response; recommended abstinence and self-help participation; and prescribed buprenorphine-naloxone.The comparison group received standard medical management and manual-based opioid dependence counseling (45-60 minute sessions). Opioid dependence counseling was based on drug counseling manuals with demonstrated efficacy, modified for this study of prescription opioid dependence treatment with buprenorphine. Counselors educated patients about addiction and recovery, recommended self-help groups, and emphasized lifestyle change. Using a skills-based format with interactive exercises and take-home assignments, opioid dependence counseling covered a wider range of relapse prevention issues in greater depth than did standard medication management, including coping with high-risk situations, managing emotions, and dealing with relationships.	Physicians certified to prescribe buprenorphine, trained substance abuse or mental health professionals10 study/treatment sites	Opioid use: urine toxicology and self-reportPhase 1 successfuloutcome: completing week 12 with opioid use on no more than 4 days in a month, absence of 2 consecutive opioid-positive urine test results, no additional substance use disorder treatment, and no more than 1 missing urine sample during the 12 weeks Phase 2 successful outcome:abstaining from opioids during week 12 and during at least 2 of the previous 3 weeks	During phase 1, only 6.6% of patients had successful outcomes, with no difference between standard medical management or standard medical management plus opioid dependence counseling. During phase 2, 49% attained successful outcomes, with no difference between groups. Success rates 8 weeks after completing the buprenorphine-naloxone taper (phase 2, week 24) dropped to 8.6%, again with no difference between groups.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Weiss, 2015[13] Prescription Opioid Addiction Treatment Study (POATS)	See above	9 month treatment; 42 month followup	375	USA; 56% male; 90% white; mean age 33 years old; 3.7% with alcohol dependence in past year; 5.9% with cannabis dependence in past year; 3.2% with cocaine dependence in past year; 3.5% with other stimulant dependence in past year; 4.8% with sedative-hypnotic dependence in past year; mean 5 years of opioid use; 22% had ever used heroin; 78% used opioids through route other than sublingually/ swallowed	Standard medication management included weekly visits with physician, combining medication administration with medication-focused counseling; phase 1 was 4-week medication taper; phase 2 for those who relapsed included medication for 12 weeks then 4-week taper Opioid dependence counseling focused on relapse prevention, skill-building, and lifestyle change opioid dependence counseling twice weekly for six weeks then once weekly for 6 weeks	Office-based; primary care; Physicians for medication management and counseling Opioid dependence counseling providers not described but appear to be physicians; research assistants conducted followup phone interviews	Followup measures: phone calls at 18, 30, and 42 months and included the Composite International Diagnostic Interview for opioid diagnosis, the ASI for substance use severity, four items from SF-36 for general health and pain, the Fagerstrom Test for Nicotine Dependence for smoking dependence severity, subset from the Pain and Opiate Analgesic Use History	Few participants had successful opioid outcomes in phase 1; almost half had successful opioid treatment in phase 2; addition of opioid dependence counseling to medication did not improve outcomes; one third of those in followup abstained and were not on agonist medication, one third were abstinent on agonist therapy and another third were using opioids (followup outcomes not described by group)

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Pharmacological Therapies								
Carrieri, 2014[14]	Induction of methadone in primary care vs. specialty care	12 months	221	France; 84% male; median age 32 years (IQR: 27-38); 27% used cocaine; 72% used street opioids; 20% used psychotropic drugs; 15% drug injection users; 64% drug snorting users; 18% were daily cannabis users; 33% had hazardous alcohol consumption; 12% history of drug overdose; 17% history of suicide attempt,;2% HIV-positive, 19% HCV-positive; 49% history of drug injection	Evaluation of implementation strategy of 14-day supervised methadone induction, with starting dose of 30-40 mg, with 10 mg increases every 2-4 days, until dose stabilization. Took into account those who switched from buprenorphine to methadone at enrollment.	Physicians in 10 sites; specialty care and primary care physicians with field experience in care for opioid dependence and/or training in care for drug dependence	Abstinence from street-opioids at 12 months using a validated question administered during phone interviews, engagement in treatment computed as the proportion of patients who actually started methadone and remained in the trial until the stabilization of dosages, retention in methadone maintenance treatment only for patients who actually started methadone treatment recorded as the time between the first day of methadone induction and the last known date that the patient was still receiving treatment, and patient satisfaction on a 5-point Likert scale that was dichotomized as very satisfied vs. other. Pharmacies and physicians recorded overdoses, signs of intoxication, and lost-to-followup. A list of 50 health-related symptoms was included in a questionnaire that helped document self-reported symptoms.	Under appropriate conditions, methadone induction in primary care is feasible and acceptable to both physicians and patients. It is as effective as induction in specialized care in reducing street-opioid use and ensuring engagement and retention in treatment for opioid dependence.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
(Carrieri 2014 pilot study) Roux, 2012[15]	See above	2 weeks induction 12 months followup for outcomes	195	Study conducted in France, no other information provided	Induction model included: 1) study-specific pretraining for primary care physicians; 2) a shared care model, based on the patient primary care physicians-Center for Substance Abuse Prevention Association -pharmacist network; 3) the exclusion of patients with triple codependence on opioids/benzodiazepines/alcohol, as screened by Mini-International Neuropsychiatric Interview; 4) the daily supervision at the local pharmacy during the initiation phase for patients starting methadone in primary care; 5) patient accountability for treatment intake and appropriate storage	Primary care and medical center; Clinic visits and phone interviews; Trained primary care and Center for Drug Abuse Prevention Association physicians	Abstinence from street-opioids at 12 months using a validated question, retention in treatment, occurrence of overdoses, prevalence of other HCV risk transmission practices, depressive symptoms using CES-D, suicidal risk using Beck Hopelessness Scale, impulsivity using the Barratt Impulsiveness Scale, sensation seeking using the Brief Sensation Seeking Scale, tobacco dependence using the Fagerstrom test, alcohol consumption using the AUDIT questionnaire, pain assessment using the Brief Pain Inventory, adherence to methadone prescription, patient-health care provider relationship, opioid withdrawal, quality of life using SF-12, adult ADHD Self-Report Scale 6 item version, urinary drug screening, and socio-demographic information on history of incarceration and contact with associations.	NR

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2001[16]	Primary care-based methadone (weekly physician sessions and monthly counseling session) vs. narcotic treatment program-based methadone (1 to 3 sessions per week dose, weekly group counseling, and monthly individual counseling)	6 months	46	USA; 65% male; 78% white; mean age 42 years; 17% HIV-positive; 91% with prior detoxification attempt; 72% with history of IV drug use	Office-based group had weekly physician contact for medication dosing and 6 take-home doses plus monthly counseling session Narcotic treatment program group had 1 to 3 treatment center visits per week for methadone dose and take-home dosing plus weekly group and monthly individual counseling Note: patients who had a positive random urine sample or urine that did not show methadone and a repeat urine sample that was positive and did not show methadone were considered clinically unstable and care was escalated	Offices of general medicine internists who provided all office-based care (4/6 were certified in Addiction Medicine); Treatment center was site of narcotic treatment program; Physicians, counselors, social workers, and employment services provided narcotic treatment program	Illicit drug use: self-report, urine and hair toxicology Patient and clinician satisfaction: 5-point Likert scale questionnaire Functional status: SF-36, ASI and modified Treatment Services Review; Depression: Center for Epidemiologic Studies Depression Scale	There was no significant between-group difference on illicit drug use or patients with clinical instability; Significantly more office-based patients thought that quality of care was excellent; There were no group differences in functional status or use of health, legal, or social services; Overall, results supported feasibility and efficacy of transferring stable opioid-dependent patients to primary care for methadone maintenance

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fudala, 2003[17]	Daily buprenorphine/naloxone vs. buprenorphine vs. placebo All participants received HIV counseling and up to 1 hour of individualized counseling per week; emergency counseling and referrals provided	4 weeks for efficacy; 48-52 weeks for safety	323 for efficacy; 472 for safety	Efficacy sample: USA; 65% male; mean age 38 years; 61% white, 28% black, 7.1% Hispanic, 1.2% Native American, 2.2% Asian/Pacific Islander; median 84 month (range: 3 to 468) duration of heroin abuse; 51% with prior enrollment in methadone or LAAM program Safety sample: USA; 69% male; mean age 39 years; 50% white, 30% black, 17% Hispanic, 0.8% native American, 1.9% Asian/Pacific Islander; median 120 months (range: 3 to 468) duration of heroin abuse; 50% with prior enrollment in methadone or LAAM program	Provided daily MAT or placebo administered on site with take-home dosing for weekends/holidays; during open-label phase, up to 10-day supply of medication provided; all participants received HIV counseling and up to 1 hour of individualized counseling per week; emergency counseling and referrals provided	Physician's office in a clinical research program distinct from methadone clinic (provider type not described)	Opiate use: percentage of opiate-negative urine samples Opiate craving: self report Overall status: per participant and per clinicianIllicit drug use other than opiates: percentage of negative urine drug screens Subject retentionRates of adverse medical events Electrocardiography and laboratory findings	Efficacy study terminated early due to greater efficacy of buprenorphine/naloxone and buprenorphine vs. placebo; Proportion of opiate-negative urine samples significantly less among both MAT groups vs. placebo; MAT groups reported significantly less opiate craving than placebo; Rates of adverse events similar in active-treatment and placebo groups; findings from open-label followup indicated combined treatment was safe and well tolerated

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
King, 2006[18]	Routine care (methadone dispensing window for weekly doses and monthly counseling for 20 minutes) vs. methadone maintenance clinic (monthly observed dose, take home supply, monthly 20 minute counseling session with medical provider) vs. primary care based-methadone (monthly observed dose, take home supply, monthly 20 minute counseling session with office physician)	12 months	92	USA; 62% male; 72% white; mean age 44 years; no patient included had submitted positive breath intoximeter readings in past year; mean 14 years of methadone treatment received over lifetime	Routine care group received 1-2 doses of methadone per week at dispensing window and 5-6 take-home doses with once-monthly appointments with the clinic counselorClinic-based methadone medical maintenance received one dose of methadone observed by nurse or physician and 27 days of take-home methadone every 4 weeks and monthly appointments with clinic counselor Office-based methadone medical maintenance received one dose of methadone observed by physician and 27 days of take-home doses every 4 weeks from physician's office and had monthly counseling session with physician Note: if found to have positive urine or failed medication recall, participant was stepped-up in care	Community primary health care center and one addiction treatment center as sites of office-based methadone medical maintenance; Physician provided medication and counseling Clinic-based methadone medical maintenance at two community-based methadone maintenance treatment programs; nurse or physician provided medication and counselor provided counseling	Illicit substance use: urine specimens Medication monitoring: random medication recalls Addiction-related issues in past 30 days: ASI Patient Satisfaction: Client Satisfaction Questionnaire Quality of therapeutic relationship: Helping Alliance Questionnaire for Patients Other measures: Post-study opinion survey Monthly hours in treatment: patient estimates of time spent engaged in treatment-based activities Engagement in employment, family/social, and personal activities: patient estimates	Generally low rates of drug use or failed medication recall with good study retention; No between-group differences on ASI scores; Treatment satisfaction was high in all groups and patients in all groups rated strong quality of therapeutic alliance; methadone medical maintenance patients in both office and clinic-based care initiated more new employment or social/family activities than routine care; most methadone medical maintenance patients reported a preference for office-based care compared with clinic-based
Lintzeris, 2004[19]	Methadone vs. buprenorphine administered under naturalistic conditions by 18 community-based and 1 specialist-based sites by general practitioners and community pharmacists (Buprenorphine Implementation trial [BIT])	12 months	139	Australia; 58% male; mean age 30 years; mean age of first heroin use 21 years; mean duration lifetime methadone treatment 27 months; 0-32% reported no heroin use in past month	Methadone treatment consistent with state guidelines with supervised dispensing at pharmacies and one take-away dose per week for stable patients; dose, frequency or review, counseling was tailored per patients; Buprenorphine treatment consisted of flexible dosing and at least monthly review, optional psychotherapy; daily dispensing at induction with alternate-day or 3-day dosing once stable	First intake of study conducted in specialist clinic; second intake of study conducted in community setting with primary care clinicians and pharmacists	Retention in treatment: pharmacy records Heroin use: Self report using Opiate Treatment Index	Among methadone stabilized patients, mean retention time was similar between groups; among heroin users, there was a trend towards improved retention among those taking methadone compared with those on buprenorphine, though this was not statistically significant; There were significant reductions in heroin use in all groups over time and a trend toward lower heroin use among heroin users on buprenorphine

ADHD = attention deficit hyperactivity disorder; ART = anti-retroviral treatment; ASI = addiction severity index; AUDIT = Alcohol Use Disorders Identification Test; BFC = behavioral family counseling; CBT = cognitive behavioral therapy; CD4 = cluster of differentiation 4 glycoprotein; CES-D = Center for Epidemiological Studies Depression; ED = emergency department; EMM = enhanced medical management; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IBT = individual based treatment; IV = intravenous; IQR = interquartile range; LAMM = levo-

alpha-acetylmethadol; MAT = medication assisted treatment; NR = not reported; OUD= opioid use disorder; PM = physician management; RNA = ribonucleic acid; SD = standard deviation; SF-12 = Medical Outcomes Study Short-Form 12; SF-36 = Medical Outcomes Study Short-Form 36; USA = United States of America; vs. = versus

Appendix H. Details of Cochrane Systematic Reviews for Guiding Question 3

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Amato, 2011[20]	To evaluate the effectiveness of any psychological plus any agonist maintenance treatment vs. standard treatment for opiate dependence	Cochrane libraries, PUBMED, EMBASE, CINAHL, PsycINFO (through June 2011)	35	OUD due to opiates (not specified); setting not described (appears mostly specialist centers); USA, Germany, Malaysia, China, Scotland	Any psychosocial intervention plus any agonist vs. any agonist alone; medical interventions were methadone, buprenorphine, LAAM; models of care not described	RCTs, CCTs	Cochrane (Higgins, 2011)	GRADE; meta-analysis done	4319	Comparing any psychosocial intervention plus maintenance pharmacological treatment to standard maintenance treatment, shows no significant advantage of adding psychosocial interventions for retention in treatment and at followup, abstinence from opiates during treatment or at followup, compliance, psychiatric symptoms, and depression. Also, there was no significant difference in outcomes comparing psychosocial approaches. Of note, standard pharmacological treatment generally offers counseling services.	Not reported	Focused on effectiveness of psychotherapy interventions in addition to standard interventions; setting not described (appears mostly specialist centers); 31 studies in USA
Ferri, 2013[21]	To evaluate efficacy of slow-release oral morphine for treatment of opioid dependence	Cochrane libraries, MEDLINE, EMBASE (through April 2013)	3	OUD due to heroin; Setting not described; Australia and Austria	Slow-release oral morphine vs. other MAT medications; models of care not described	RCTs, quasi-randomized (one study only provided conference abstract)	Cochrane (Higgins, 2011)	GRADE; no meta-analysis	195	Limited evidence that sustained-release oral morphine is at least similar to other MAT medications for retention and other clinical outcomes	Limited evidence of no major differences in adverse events	Focused on effectiveness of medications; trials with no description of setting; no studies in USA

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Gowing, 2011[22]	To assess the effect of oral substitution treatment for opioid dependent injecting drug users on risk behaviors and rates of HIV	Cochrane libraries, MEDLINE, EMBASE, psycINFO (through May 2011)	38	OUD due to heroin; majority injecting drug users or with recent history (last 3 months); users of other injectable drugs also included; mostly specialist treatment centers; USA, UK, Australia, Italy, Germany, Canada, Malaysia, Ukraine with one study in multiple countries	Buprenorphine, methadone, or LAAM for substition therapy (alone or vs. others); models of care not described	RCTs, observational prospective studies, cross-sectional studies	Cochrane (Higgins, 2008)	Unclear for quality; No meta-analysis	12400	Oral substitution treatment with methadone or buprenorphine is associated with significant reductions in illicit opioid use, injecting use, and sharing of injecting equipment; also led to fewer drug users reporting multiple sex partners or exchanges of sex for money or drugs but no change in condom use; reduced drug risk behaviors led to reduced HIV; one study partially done in primary care showed significant reductions in proportion injecting, sharing injecting equipment, and having unprotected sex in those on methadone treatment.	Not reported	Focused on effectiveness of medications on HIV and behaviors; 2 studies included primary care settings; 26 studies in USA

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Lobmaier, 2008[23]	To evaluate the effectiveness of sustained-release naltrexone for opioid dependence and its adverse effects in different populations	Cochrane libraries, MEDLINE, EMBASE, CINAHL, LILACS, PsycINFO, ISI Web of Science, clinicaltrials.gov (through November 2007)	1 for effective-ness; 10 for safety in OUD	OUD not specified; effectiveness study in outpatient setting; Australia, Germany, USA, Norway, Spain, UK	Three depot and two implant formulations of naltrexone (10 of 17 depot studies used sustained release form) vs. placebo, different naltrexone doses, oral naltrexone, or methadone; in addition to medication, all patients offered relapse prevention therapy	RCTs for effectiveness; prospective controlled and uncontrolled trials, case-series, and record-linkage for safety evaluation	Cochrane (Higgins, 2006)	Unclear for quality; meta-analysis done for safety	60 for effectiveness; mean 168 (range: 5 to 894) for safety in OUD	One study found high-dose naltrexone depot injections significantly increased days in treatment vs. placebo and vs. low-dose with no group differences on patients retained in treatment;	Limited data showing side effects were significantly more frequent in naltrexone depot groups vs. placebo (mostly site-related); among OUD, no significant group differences in adverse events; most studies lacked systematic assessment of side effects and adverse events were rare	Focused on effectiveness and adverse events of medications; effectiveness study in outpatient setting (no further details); effectiveness study and most safety studies done in USA

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Mattick, 2009[24]	To evaluate the effects of methadone maintenance treatment compared with other treatment that did not involve opioid replacement therapy for opioid dependence	Cochrane libraries, EMBASE, PUBMED, CINAHL, Current Contents, PsycLIT, CORK, Alcohol and Drug Council of Australia, Australian Drug Foundation, Centre for Education and Information on Drugs and Alcohol, Australian Bibliographic Network, Library of Congress (through December 2008)	11	OUD due to opioids (not specified); most studies done in specialist medical or research facilities (3 in prison setting); USA, Australia, Hong Kong, Thailand, Sweden	Methadone maintenance vs. placebo or other nonpharmacological therapy (wait-list control, drug-free rehabilitation, detoxification); models of care not described (some studies included counseling in the intervention but this was not described)	RCTs	Cochrane - focus on randomization	GRADE; meta-analysis done	1969	Methadone was significantly more effective than nonpharmacological approaches in treatment retention and suppression of heroin use but not different in criminal activity or mortality	Not reported	Focused on effectiveness of medication; no studies appear to be have been done in primary care; 6 studies in USA

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Mattick, 2014[25]	To evaluate buprenorphine maintenance compared to placebo and to methadone maintenance in the management of opioid dependence, including its ability to retain people in treatment, suppress illicit drug use, reduce criminal activity, and mortality	Cochrane libraries, MEDLINE, EMBASE, Current Contents, PsycLIT, CORK, Alcohol and Drug Council of Australia, Australian Drug Foundation, Centre for Education and Information on Drugs and Alcohol, Library of Congress (through January 2013)	31	OUD due to heroin or other opioids; setting not described; North America, Europe, Asia, Middle East, Australia	Buprenorphine maintenance vs. placebo or methadone; models of care not described	RCTs	Cochrane (Higgins, 2011)	GRADE; meta-analysis done	5430	Buprenorphine was superior to placebo in participant retention at all doses; only high-dose buprenorphine (not low- or moderate-dose) was more effective than placebo in suppressing illicit opioid use; flexible dosed buprenorphine was less effective than methadone in participant retention with no group differences in suppression of opioid use; low-dose methadone was more likely to retain participants and limit opioid use than low-dose buprenorphine but high and medium-dose methadone were not more effective than high and medium-dose buprenorphine for participant retention and illicit opioid use	Limited evidence of no significant differences between methadone and buprenorphine (one result of more sedation among methadone users)	Focused on effectiveness of medications; setting not described; 15 studies from North America

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Minozzi, 2009[26]	Among adolescents (13-18 years old), to assess the effectiveness of any maintenance treatment alone or in combination with psychological intervention compared to no intervention, other pharma-cological or psychosocial intervention on retaining adolescents in treatment, reducing substance use, and reducing health and social status	Cochrane libraries, MEDLINE, EMBASE, CINHAL (through August 2008)	2	OUD due to heroin; outpatient; USA	Methadone maintenance vs. LAAM; buprenorphine-naloxone maintenance vs. buprenorphine detoxification; models of care not described	RCTs and controlled clinical trials	Cochrane (Higgins, 2008)	GRADE; no meta-analysis	187	Limited evidence that maintenance treatment was superior in patient retention but not in reducing illicit opioid use; Opioid use at 1 year followup was significantly lower in the maintenance group and more patients in this group were enrolled in other addiction treatment at followup	Limited evidence of no serious side effects or withdrawals attributable to bupren-orphine-naloxone	Focused on effectiveness of medications; outpatient setting (unclear if primary care); all trials done in USA

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Minozzi, 2011[20]	To evaluate the effects of naltrexone maintenance treatment vs. other treatments/ placebo in preventing relapse in opioid addicts after detoxification	Cochrane libraries, PubMed, CINAHL (through June 2010)	13	OUD due to heroin alone or multiple drugs; outpatient only; USA, Israel, Russia, Italy, Spain, China, Malaysia, Germany	Oral naltrexone alone or in combination with psychosocial treatments vs. placebo, no intervention, other pharmacological treatments, or psychosocial treatments; models of care not described	RCTs	Cochrane (Higgins, 2008)	GRADE (ratings not shown); meta-analysis	1158	Oral naltrexone did not perform better than treatment with placebo or no agent with respect to abstinence and relapse, though naltrexone was favored for number of people reincarcerated. Naltrexone was not superior to benzodiazepines and buprenorphine for retention, abstinence, and side effects, though numbers retained in studies were generally low. In single study of naltrexone vs. psychotherapy, there was no statistically significant difference for abstinence and reincarceration. Overall, studies inadequate to evaluate oral naltrexone treatment for opioid dependence.	Limited evidence of no significant differences in adverse events	Focused on effectiveness of medications /interventions; includes psychotherapy as an intervention; outpatient trials (unclear if primary care); 4 trials in USA

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Minozzi, 2013[27]	Among pregnant women, to assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological or psychosocial interventions for child health status, neonatal mortality, treatment retention, and reducing substance use	Cochrane libraries, PUBMED, CINAHL (through September 2013)	4	Opiate addicted pregnant women (OUD not specified); inpatient and outpatient settings; Austria, USA, one multicounty trial (Austria, Canada, USA)	Methadone vs. buprenorphine or slow-release morphine; models of care not described	RCTs	Cochrane (Higgins, 2011)	GRADE; meta-analysis done	271	Limited evidence of no significant differences between methadone and buprenorphine or slow-release morphine for all outcomes	One study showed no difference in side effects for the mother using methadone vs. buprenorphine and significantly less side effects for the infant on buprenorphine; one study showed no difference in side effects for the mother using methadone vs. slow-release morphine with one child in each group experiencing a serious side effect (apnea)	Focus on effectiveness of medications; 3 studies in outpatient setting (no further details); 2 studies done in USA

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Rahimi-Movaghar, 2013[28]	To evaluate the effectiveness and safety of various pharma-cological therapies on maintenance of opium dependence (alone or in combination with psychosocial interventions)	Cochrane libraries, MEDLINE, EMBASE, CINAHL, PsychINFO, regional databases (IMEMR and ASCI), national databases (Iranmedex and Iranpsych); through February 2012	3	OUD due to heroin; outpatient; Iran	Different doses of buprenorphine compared; one study of baclofen vs. placebo for maintenance post detoxification; models of care not described	RCTs	Cochrane (Higgins, 2011)	Unclear for quality; no meta-analysis	870	Higher doses of buprenorphine significantly increased the treatment retention rate compared with lower doses; No significant difference in maintenance retention rate between baclofen vs. placebo post detoxification.	Not reported	Focused on effectiveness of medications; outpatient setting (unclear if primary care); no trials in USA (appears Asia-focused)

CCTs = controlled clinical trials; GRADE = Grading of Recommendations; Assessment; Development and Evaluations; HIV = human immunodeficiency virus; LAMM = levo-alpha-acetylmethadol; MAT = medication-assisted treatment; OUD = opioid use disorder; RCT = randomized controlled trial; UK = United Kingdom; USA = United States of America; vs. = versus

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